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Synthesis of type 2 Lewis antigens via novel regioselective glycosylation of an orthogonally protected lactosamine diol derivative

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Abstract

The novel and efficient synthesis of type 2 Lewis antigens is reported in this study. The rationally designed lactosamine-3,2′-diol derivative with an orthogonal set of protecting groups is efficiently glycosylated with a benzyl protected 1-thio-L-fucoside donor in a unique regioselective manner to produce Lewis x (Le^x) and Lewis y (Le^y) derivatives in good yields. These derivatives can be prepared not only exclusively but also synchronously by choosing the appropriate reaction temperature and donor-acceptor molar ratio. The Le^x derivatives are easily converted into sulfated or non-sulfated Le^x bearing a terminal azido functionalized oligo-(ethyleneoxide) linker; the Le^y derivative having the same linker can also be prepared, all of which can be further used for the chemical modification of other compounds and materials.

Keywords: Type 2 Lewis antigens; Sulfated Lewis x; Lewis y; Regioselective glycosylation; The Heyns rearrangement

1. Introduction

Lewis antigens are well-known as glycan-based blood group antigens,[1] which are classified as type 1 and type 2, depending on the disaccharide core structure. Type 1 Lewis antigens, Lewis a and Lewis b, have a common backbone [→3Galβ(1→3) GlcNAcβ1→] and exist widely in the membrane of erythrocytes. The type 2 core structure [→3Galβ(1→4) GlcNAcβ1→] is also found

in numerous glycoconjugates; however, the distribution of its fucosylated derivatives, Lewis x (Le^x) and Lewis y (Le^y), classified as type 2 Lewis antigens (T2-LAs), is limited to some epithelial cells and leukocytes. Notably, T2-LAs are overexpressed in various tumor cells,[2] and are thus frequently used as biomarkers for the diagnosis of cancer. Furthermore, these T2-LAs are sometimes found in their sulfated form, which includes a 6-*O*-sulfo-GlcNAc residue.[3] The Le^x determinant also plays a critical role in various biological events such as inflammation, lymphocyte homing, and infection of pathogens.[4] Thus, T2-LAs have attracted much attention as promising target compounds for cancer therapy as well as for the treatment of inflammation, infectious diseases, etc.

In order to utilize T2-LAs and their derivatives as bioactive compounds, it is essential to establish versatile, widely applicable synthetic methods. A large number of reports on the synthesis of Lewis antigens have been published to date;[5] however, none of them have reported the use of common key intermediates to construct T2-LAs, including their sulfated form. In the present study, we report the successful and rapid assembly of T2-LAs (**3**–**5**) via a refined disaccharide key intermediate **2**, which can be readily prepared from lactulose **1** through the Heyns rearrangement method[6] (Figure 1). This method is very convenient to obtain useful 2-amino-2-deoxy sugars, particularly lactosamine derivatives.[7]

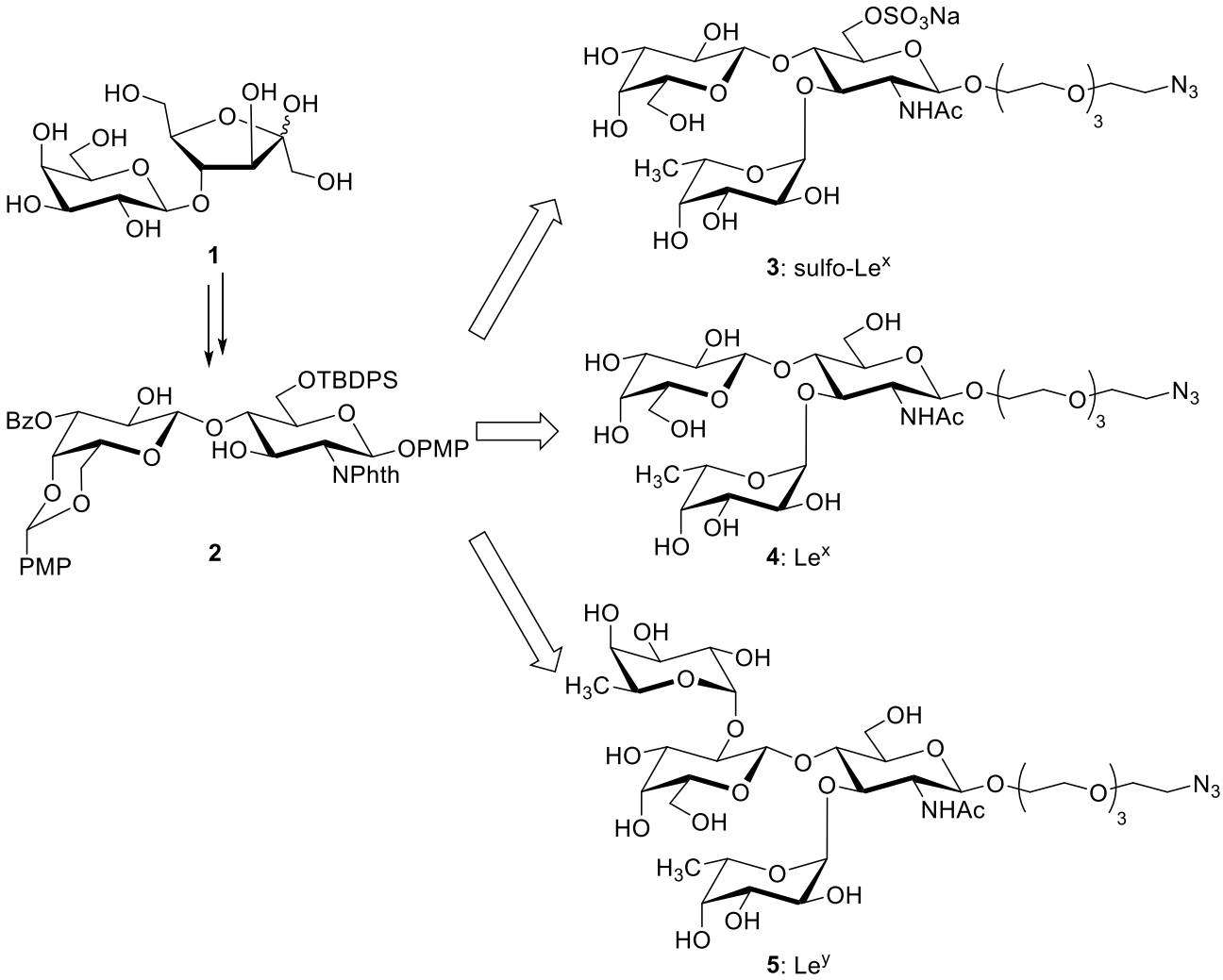


Figure 1. Efficient synthesis of T2-LAs (**3**–**5**) via the refined orthogonally protected T2 disaccharide derivative **2** derived from lactulose **1**.

2. Results and discussion

2.1 Refinement of the molecular design of key intermediate 2

In a previous paper,[8] we reported the synthesis of T2-LAs having a set of orthogonal protecting groups via the useful disaccharide intermediate **2′** (Figure 2). Compound **2′** was found to be an excellent intermediate for the synthesis of T2-LAs, but had a major drawback concerning the

removal of the anomeric 4-methoxyphenyl (PMP) group: the 6-*O*-*tert*-butyldimethylsilyl (TBDMS) group was found to be labile under oxidation conditions by cerium(IV) ammonium nitrate (CAN). It is acceptable to produce neutral, non-sulfated T2-LAs; however, in order to synthesize structurally complicated and highly bioactive sulfated T2-LAs, the protecting group at glucosamine C6 must be stable under oxidation conditions. Thus, we refined the molecular design from **2′** to **2**: the stability of the *tert*-butyldiphenylsilyl (TBDPS) group is several hundred times higher than that of TBDMS under acidic conditions, whereas both show similar susceptibility to tetra-*n*-butylammonium fluoride (TBAF).[9] Therefore, TBDPS was selected as a more suitable protecting group for the C6 position of the glucosamine residue. Further, the 4,6-*O*-benzylidene protecting group for the Gal residue was replaced with the *p*-methoxybenzylidene group, which is more rapidly removed by hydrogenolysis.

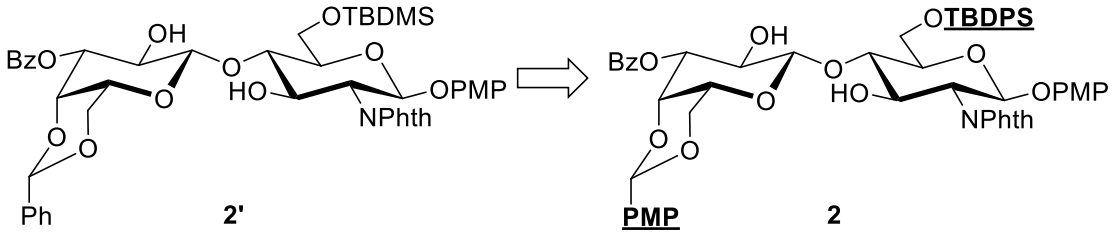
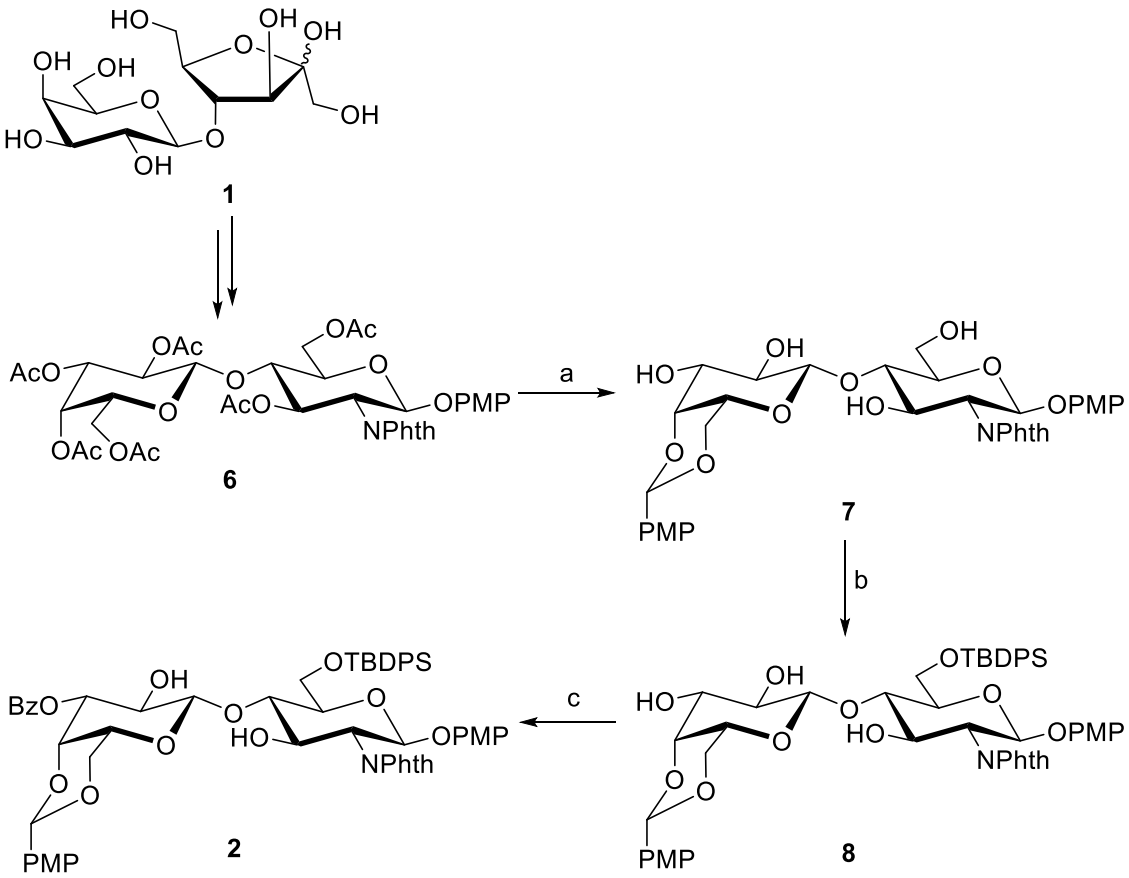


Figure 2. Refinement of the molecular design of key intermediate **2**.

According to our previous report,[8] the lactosamine derivative of **6** was readily prepared from lactulose **1** via the Heyns rearrangement (Scheme 1). After removal of the acetyl protecting groups in **6**, the 4′- and 6′-hydroxy moieties were protected with a *p*-methoxybenzylidene group to afford **7** in 69% yield via a two-step procedure. The 6-OH moiety in **7** reacted selectively with TBDPS-Cl

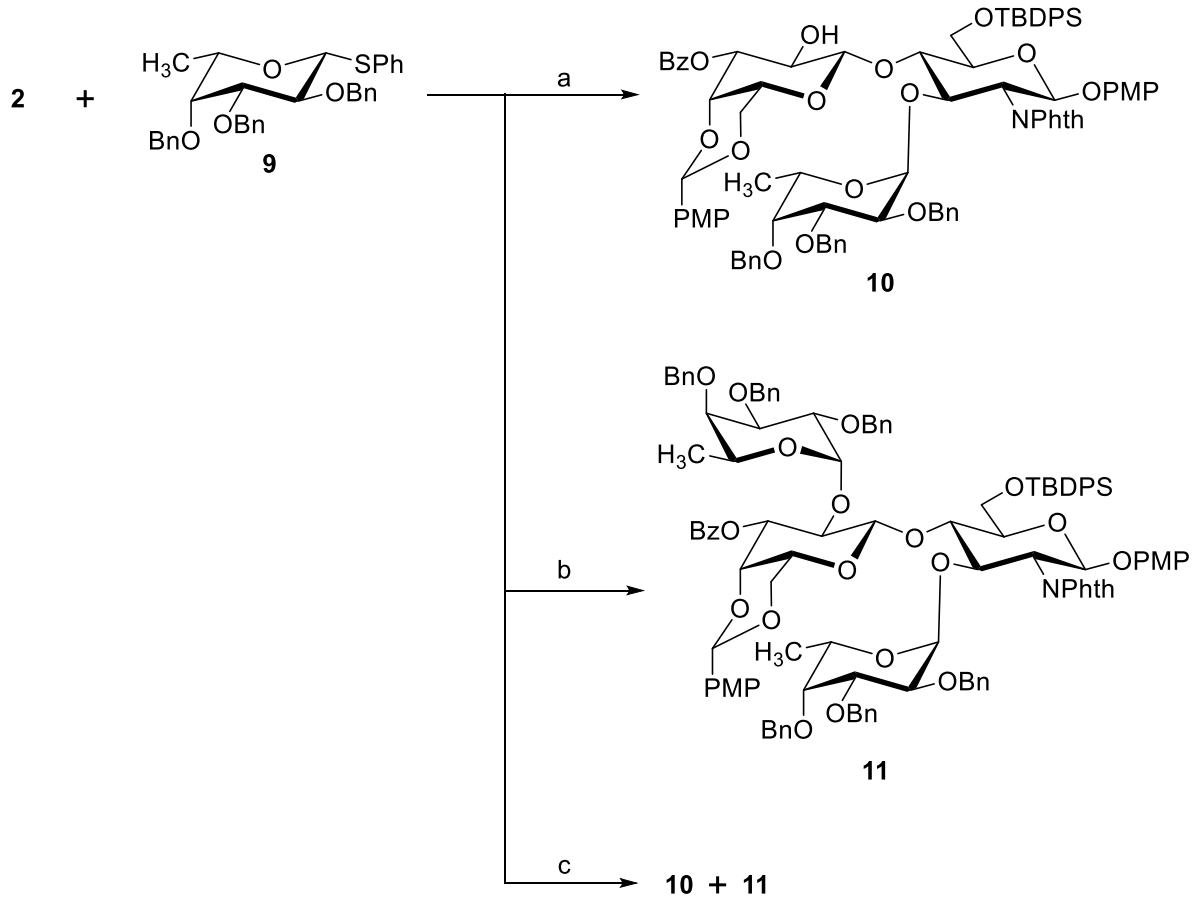
in pyridine, giving **8** in moderate yield (59%). We originally controlled the selectivity in the regioselective 3′-*O*-benzoylation by lowering the reaction temperature (−50 °C). However, the unfavorable 3,3′-di-*O*-benzoyl product was formed even under the optimized conditions designed to obtain the target 3′-mono-*O*-benzoyl product. In the present study, we exclusively obtained the target product **2** at ambient temperature in 73% yield by employing a metal-coordinated regio- and chemoselective nucleophilic substitution method.[10]



Scheme 1. Reagents and conditions: (a) 1) MeONa / MeOH, 2) *p*-anisaldehyde dimethylacetal, (±)-10-camphorsulfonic acid/DMF, 30 °C, 24 h, 69% (2 steps); (b) TBDPS-Cl/pyridine, rt, 64 h, 59%; (c) Bu_2SnCl_2, PEMP, BzCl/THF, rt, 48 h, 73%. NPhth: phthalimido, PMP: 4-methoxyphenyl, PEMP: 1,2,2,6,6-pentamethylpiperidine.

2.2 On demand synthesis of Le^x and Le^y derivatives by regioselective α-fucosylation of 2

Glycosylation of **2** with benzyl-protected phenyl 1-thio-L-fucopyranoside (**9**)[11] is the extremely unique reaction throughout the synthesis of T2-LAs (Scheme 2). In order to obtain the Le^x derivative **10**, the glycosylation was carried out at lower temperature (−78 °C) with a slight excess of **9** over **2**; under these conditions, **10** was isolated as the sole product in 76% yield (Table 1, entry 1). Le^y derivative **11** was exclusively formed in 83% yield when more than twice the amount of **9** (2.4 eq) relative to **2** was used at a higher temperature of −40 °C (entry 2). The synchronous synthesis of **10** and **11** using **9** and **2** (entries 3 and 4) is worth mentioning. Compound **11** appeared at a higher temperatures (−40 °C or −50 °C) than that in entry 1. Furthermore, both **10** and **11** were obtained efficiently in 49% and 45% yields, respectively, using an excess amount of **9** (1.8 eq) at −40 °C (entry 4). These results indicate that the synthesis of **10** and **11** can be finely controlled by varying the reaction temperature and the feed ratio. Notably, compounds **10** and **11** can be easily separated by conventional silica gel column chromatography: the R_f values for **10** and **11** in an *n*-hexane–EtOAc 2:1 mixture are 0.28 and 0.44, respectively.



Scheme 2. On demand and synchronous syntheses of Le^x and Le^y derivatives via glycosylation of **2** with **9** under the reaction conditions summarized in Table 1.

Table 1. One-pot synthesis of **10** and **11** under different reaction conditions.[a]

entry	path	**2**/eq	**9**/eq	NIS/eq	TfOH/eq	T/°C	time/h[b]	yield/%	
								10	**11**
1	a	1.0	1.2	2.5	0.2	−78	1.0	76	n.d.[c]
2	b	1.0	2.4	5.0	0.4	−40	3.0	n.d.[c]	83
3	c	1.0	1.2	2.5	0.2	−50	2.0	25	16
4	c	1.0	1.8	2.5	0.2	−40	1.0	49	45

[a]Reaction was carried out under the indicated conditions, in CH_2Cl_2–Et_2O using the NIS–TfOH

activation system. [b]Time for complete consumption of **9**. [c]Not detected.

It is very intriguing that the reactivity of the two hydroxy groups in **2** is strictly fixed as 3-OH > 2′-OH: a mono-fucosylated product at 2′-OH, that is, a type 2H [Fucα(1→2)Galβ(1→4)GlcNAcβ1→] derivative is not formed at all in this series of reactions. These results are consistent with our previous report,[8] although the molecular design of acceptor **2** is slightly different from that of **2′**. Thus, the combination of the newly designed diol acceptor **2** and donor **9** has proved to be highly effective for not only the selective synthesis of Le^x or Le^y derivatives but also the synchronous synthesis of both derivatives in a one-pot reaction. Although there are a few reports on lactosamine diol derivatives for the synthesis of T2-LAs,[12] the order of reactivity of the two hydroxy groups in these derivatives is 2′-OH > 3-OH without exception, which is opposite to that for **2** and renders the preparation of Le^x derivatives difficult. Therefore, compound **2** is the most effective acceptor capable of providing both Le^x and Le^y derivatives when using **9** as the donor.

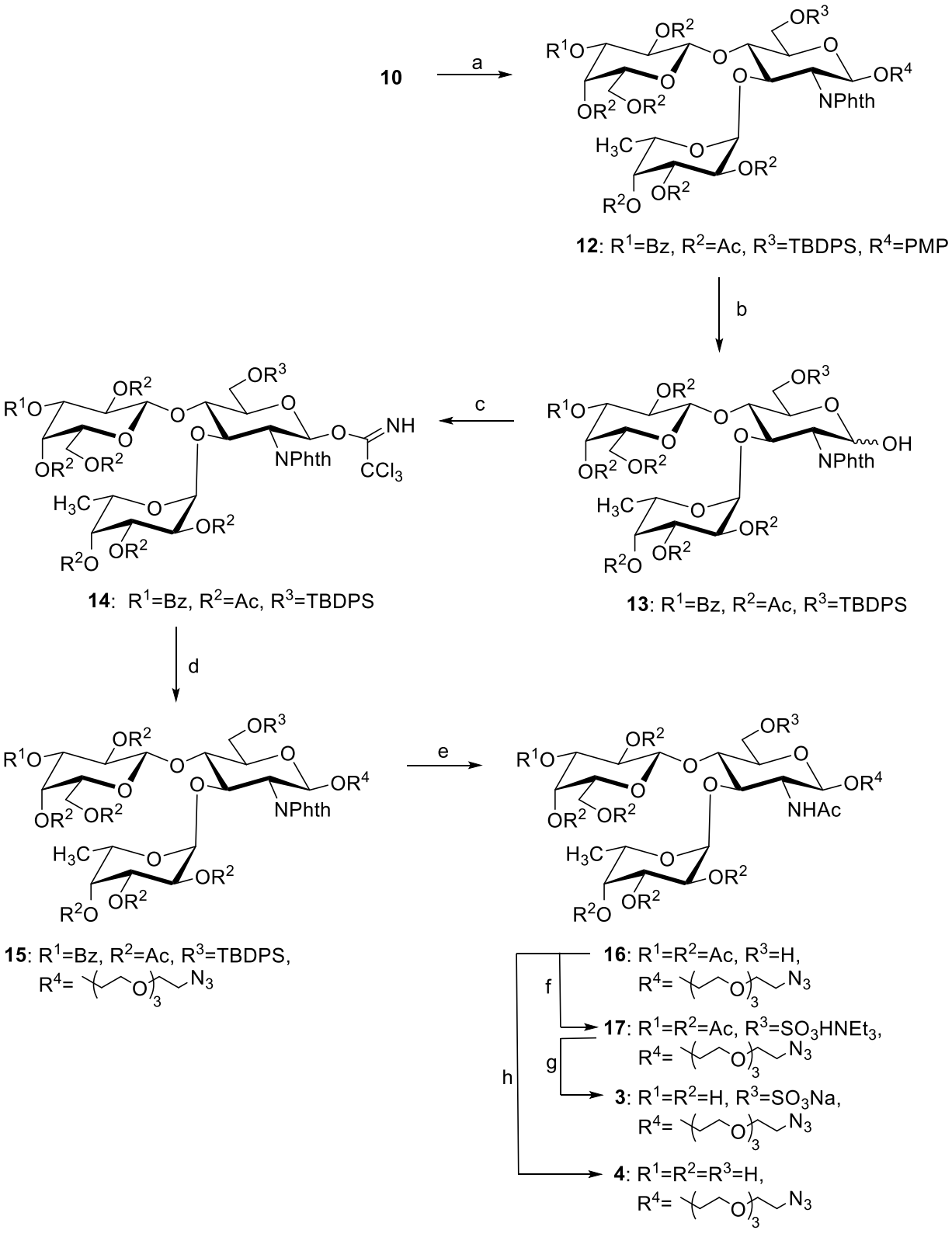
2.3 Synthesis of 6-O-sulfo-Le^x 3 and non-sulfated Le^x 4 bearing a terminal azido functionalized oligo-ethyleneoxide linker

For future applications of T2-LAs, we introduced a terminal azido functionalized aglycon moiety. A highly hydrophilic oligo-(ethyleneoxide) structure is advantageous for conjugation with

all kinds of bioactive compounds such as proteins, lipids, polysaccharides, and synthetic polymers. Furthermore, azides are the first choice in current biochemical and materials sciences as they allow conjugation with a range of substances having alkyne groups via a Huisgen cycloaddition ("click chemistry").[13,14] Hence, we selected a 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl group as an efficient linker for T2-LAs, as shown in Fig. 1.

Two types of Le^x derivatives (**3** and **4**) were synthesized following the reactions outlined in Scheme 3. In order to avoid damaging the α-L-fucoside linkage and azido group, hydrogenation of **10** was first carried out with $Pd(OH)_2$ on activated carbon ($Pd(OH)_2$-C) under H_2 atmosphere. This reaction normally proceeds to completion within 10 h, and the reaction mixture must be immediately worked-up, as prolonged reaction accelerates the undesirable cleavage of the α-L-fucoside linkage due to the acidity of the reagents. After acetylation, compound **12** was obtained in 39% yield, in two steps. Considering the low yield and our observations by TLC monitoring during the hydrogenation, removal of the benzyl protection in **11** without cleaving the α-L-fucoside linkage seems difficult. The anomeric PMP group of **12** was smoothly removed by CAN oxidation to produce **13** in 61% yield. Compound **13** was converted into the activated glycosyl donor of trichloroacetimidate **14** through the reaction of trichloroacetonitrile with DBU in 83% yield. The linker moiety was introduced through the glycosylation of 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-1-ethanol with **14**, promoted by the addition of TMSOTf at −50 °C, affording **15** in a modest yield of 48%. The acyl groups in **15** were removed successively by treatment with MeONa and hydrazine

monohydrate, followed by acetylation in pyridine and the removal of the TBDPS group with TBAF, affording **16** in 56% yield (4 steps). Sulfation at the 6-OH group in **16** was carried out by the addition of $SO_3 \cdot NMe_3$ to produce **17** in excellent yield (91%). Finally, all of the *O*-acetyl groups in **17** were removed with MeONa, which resulted in the target 6-*O*-sulfo-Le^x **3** in 63% yield. The non-sulfated Le^x derivative **4** was obtained from **15** through the reactions in steps e and h in 15% yield (5 steps). Thus, the sulfated and non-sulfated forms of the Le^x derivatives were efficiently synthesized from a common intermediate, **10**, which could be readily prepared through the regioselective glycosylation described above.



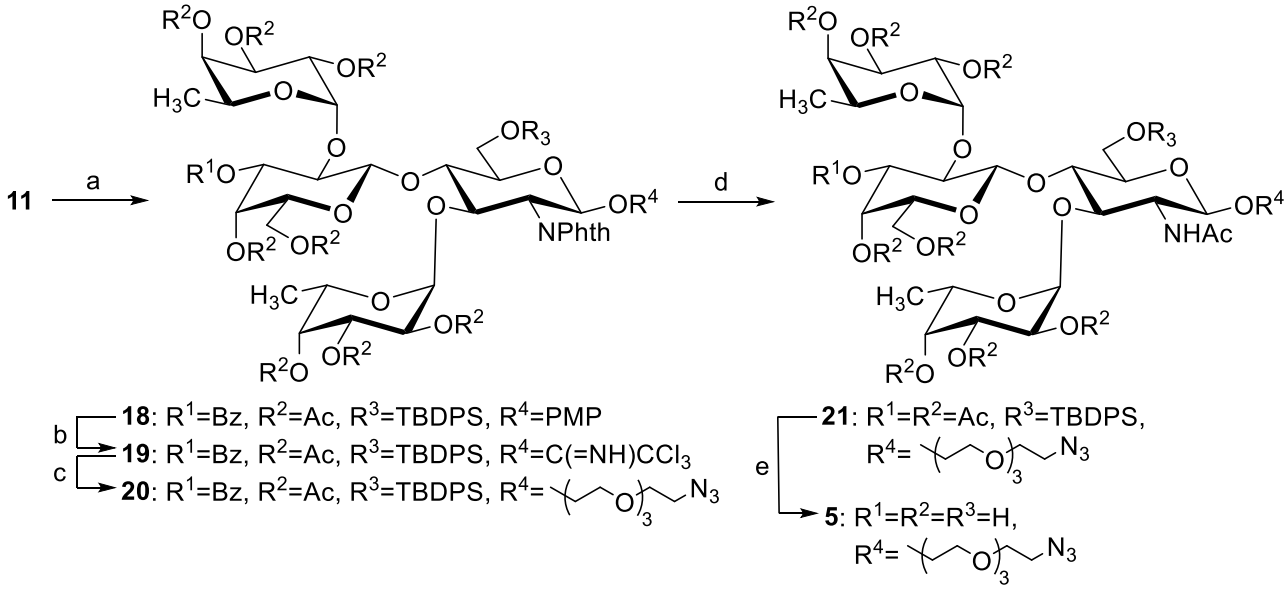
Scheme 3. Reagents and conditions: (a) (1) $Pd(OH)_2$-C, H_2/MeOH, rt, 10 h, (2) Ac_2O/pyridine, rt, overnight, 39% (2 steps); (b) CAN/CH_3CN–H_2O, 0 °C, 6 h, 61%; (c) CCl_3CN, DBU/CH_2Cl_2, 0 °C, 5

h, 83%; (d) $HO(CH_2CH_2O)_3C_2H_4N_3$, TMSOTf, MS4A/CH_2Cl_2, −50 °C, 8 h, 48%; (e) (1) MeONa/MeOH, rt, overnight, (2) $NH_2NH_2·H_2O$/EtOH, 90 °C, 7 h, (3) Ac_2O/pyridine, rt, 48 h, (4) TBAF–AcOH/THF, rt, 72 h, 56% (4 steps); (f) $SO_3·NMe_3$/DMF, 55 °C, 72 h, 91%; (g) MeONa/MeOH, rt, overnight, 63%; (h) MeONa/MeOH, rt, overnight, 15% (5 steps from **15**).

2.4 Synthesis of Le^y bearing a terminal azido functionalized oligo-ethyleneoxide linker 5

The Le^y derivative bearing a terminal azido functionalized oligo-ethyleneoxide linker **5** was also prepared according to the reactions outlined in Scheme 4. Compound **11** was treated with $Pd(OH)_2$-C in THF–MeOH (1:1) mixture under H_2 atmosphere as described for the synthesis of **12**. The obtained mixture was subjected to acetylation to provide pure **18**. The anomeric PMP group in **18** was removed by CAN oxidation, followed by trichloroacetimidation to give **19**. Glycosidation of **19** with 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-1-ethanol, which is the same acceptor employed in the synthesis of **15**, proceeded very smoothly with the addition of a catalytic amount of TMSOTf at −50 °C and gave **20** within 30 min in a very good yield of 80%. Compound **20** was converted into **21** through a three-step reaction, i.e., removal of the acetyl and benzoyl groups by MeONa, removal of the phthaloyl group by hydrazine monohydrate and acetylation, which gave **21** in 64% yield. All the protecting groups in **21** were removed by successive treatment with TBAF in THF and MeONa in MeOH, which led to the target Le^y derivative **5** in 57% yield via two steps. Thus, the Le^y derivative can also be synthesized easily from **11**, which in turn can be obtained by the glycosylation

described above.



Scheme 4. Reagents and conditions: (a) (1) $Pd(OH)_2$-C, H_2/THF–MeOH, rt, 10 h, (2) Ac_2O, DMAP/pyridine, rt, 24 h, 68% (2 steps); (b) (1) CAN/CH_3CN–H_2O, rt, 2 h, (2) CCl_3CN, DBU/CH_2Cl_2, 0 °C, 4 h, 56% (2 steps); (c) $HO(CH_2CH_2O)_3C_2H_4N_3$, TMSOTf, MS4A/CH_2Cl_2, −50 °C, 0.5 h, 80%; (d) (1) MeONa/MeOH, rt, 2 h, (2) $NH_2NH_2·H_2O$/EtOH, 90 °C, 13 h, (3) Ac_2O/pyridine, rt, overnight, 64% (3 steps); (e) (1) TBAF/THF, rt, 72 h, (2) MeONa/MeOH, rt, overnight, 57% (2 steps).

3. Conclusion

In the present study, we have demonstrated for the first time the feasibility of the on-demand synthesis of Le^x and Le^y derivatives, in addition to their synchronous synthesis in one-pot through the combined use of diol acceptor **2** and benzyl-protected thiophenyl fucoside donor **9**. The

selectivity was easily controlled by varying the reaction temperature and the ratio of **2** and **9**. The derivatives of Le^x and Le^y were further functionalized by introducing an oligo-ethyleneoxide-azide linker through glycosylation. The versatile set of orthogonal protecting groups of the obtained Le^x derivative **15** enabled the facile and regioselective synthesis of both sulfated Le^x **3** and non-sulfated Le^x **4**. Le^y derivative **5** was also easily prepared from **11**. Thus, our method is highly efficient for the synthesis of T2-LAs and will be further applied to the preparation of a variety of bioactive materials.

4. Experimental

4.1 General methods

Anhydrous solvents were purchased from Wako Pure Chemical Industries, Ltd., and stored under Ar atmosphere prior to use. Other chemicals were used without further purification unless otherwise stated. Molecular sieves (MS) AW300 and 4A were powdered and activated over 100 °C under reduced pressure with P_2O_5 as desiccant prior to use. Silica gel flash column chromatography was performed on Silica Gel 60, spherical, neutrality (Nacalai Tesque), or with a CombiFlash Rf 75 Var (Teledyne Isco) on RediSep Rf Gold Normal Phase Silica columns. The reactions were monitored by TLC (silica gel 60 F254, Merck) visualized by sprayed with a mixture of $H_3(PMo_{12}O_{40})\cdot n\,H_2O$ (12.5 g) and $Ce(SO_4)_2\cdot nH_2O$ (5 g) in 10% H_2SO_4 (500 mL) and colored by heating at 140 °C. Glycosylation reactions at −50 °C or lower were performed on UCR-150

(Techno-sigma). Optical rotations were measured with a P-1010 polarimeter (Jasco). ^{1}H and ^{13}C NMR were recorded on a DPX-400 spectrometer (Bruker). Assignments were based on homo- and heteronuclear correlation measurements, and DEPT measurements. High resolution mass spectrometry was carried out with JMS-HX110A spectrometer (Jeol, for FAB-MS) or Exactive spectrometer (Thermo Fisher Scientific, for ESI-MS). Melting points were determined with a MP-500P (Yanaco).

4.2. 4-Methoxyphenyl 4,6-*O*-(4-methoxybenzylidene)-*β*-D-galactopyranosyl-(1→4)-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (7).

Compound **6**[8] (13.5 g, 16.2 mmol) in dry MeOH (250 mL) was treated with MeONa in MeOH (ca. 28wt%, 2.4 mL) at 0 °C under dry atmosphere for 23 h. The formed precipitate was filtered through filter paper, and washed with MeOH. The filtrate was neutralized by addition of Dowex 50W-X8 (H^+ form), filtered through a cotton bed, and concentrated to dryness by vacuum pump overnight. The former precipitate and the latter residue were combined and dissolved in dry DMF (120 mL). To a solution of the mixture was added *p*-anisaldehyde dimethylacetal (3.16 mL, 18.6 mmol) under acidic conditions in the presence of catalytic amount of (±)-10-camphorsulfonic acid. After kept stirring at rt for 7 h, excess amount of Et_3N was added to neutralize the reaction system. The mixture was concentrated under diminished pressure, and coevaporated with toluene. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 20:1, v/v, containing 0.5% Et_3N) to provide **7**

(7.75 g, 11.1 mmol, 69 %) as a white solid.

$[\alpha]_D^{23}$ −20.8 (*c* 0.64, $CHCl_3$); mp 128–130 °C ; R_f 0.30 ($CHCl_3$/MeOH, 10:1); ^{1}H NMR (400 MHz, CD_3OD, TMS): δ (ppm) 7.96–7.78 (m, 4H, N*Phth*), 7.47–6.72 (m, 8H, -C_6H_4-OMe×2), 5.70 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1^{I}), 5.56 (s, 1H, C*H* of *p*-methoxybenzylidene), 4.55 (d, 1H, $J_{1,2}$ 7.5 Hz, H-1^{II}), 4.51 (dd, 1H, $J_{2,3}$ 11.0, $J_{3,4}$ 8.5 Hz, H-3^{I}), 4.28 (dd, 1H, $J_{1,2}$ 8.6, $J_{2,3}$ 11.0 Hz, H-2^{I}), 4.24–4.06 (m, 3H, H-4^{II}, H-6^{II}a, H-6^{I}a), 4.06–3.93 (m, 2H, H-6^{II}b, H-6^{I}b), 3.84 (t, 1H, $J_{3,4}$=$J_{4,5}$=9.6 Hz, H-4^{I}), 3.77 (s, 3H, O*Me*), 3.73–3.63 (m, 7H, H-5^{I}, H-2^{II}, H-3^{II}, H-5^{II}, O*Me*) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.23, 167.93 (*C*=O), 159.89, 155.21, 150.79, 134.03, 131.58, 130.38, 127.76, 123.32, 118.32, 114.32, 113.30 (aromatic), 103.99 (C1^{II}), 100.92 (*C*H of *p*-methoxybenzylidene), 97.45 (C1^{I}), 81.92 (C4^{I}), 75.53 (C4^{II}), 75.05 (C5^{I}), 72.08 (C3^{II}), 70.58 (C2^{II}), 69.70 (C3^{I}), 68.73 (C6^{II}), 66.82 (C5^{II}), 61.54 (C6^{I}), 56.07 (C2^{I}), 55.47, 55.17 (O*Me*); HRMS (FAB, positive ion mode, NBA) *m*/*z* = 718.2103 [M + Na]$^+$, calcd for $C_{35}H_{37}NO_{14}Na$, 718.2112.

4.3. 4-Methoxyphenyl 4,6-*O*-(4-methoxybenzylidene)-*β*-D-galactopyranosyl-(1→4)-6-*O*-*tert*-butyldipheylsilyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (8).

To a solution of **7** (7.75 g, 11.1 mmol) in anhydrous pyridine (120 mL) was added *tert*-butyldiphenylchlorosilane (5.36 mL, 20.9 mmol) at rt under dry atmosphere. After stirring for 64 h, MeOH was added to quench excess reagent, and then the mixture was concentrated under reduced pressure. The residue was coevaporated with toluene and extracted with $CHCl_3$, washed

successively with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed and concentrated under diminished pressure. The residue was subjected to silica gel column chromatography eluting with $CHCl_3$/EtOAc (2:1, v/v, containing 0.1% Et_3N) to provide pure **8** (6.12 g, 6.55 mmol, 59 %) as an amorphous powder.

$[\alpha]_D^{23}$ −20.6 (*c* 1.0, $CHCl_3$) ; R_f 0.33 ($CHCl_3$/EtOAc, 1:1), ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.96–6.68 (m, 22H, N*Phth*, -OSi*Ph*$_2$CMe$_3$, -C$_6$*H*$_4$OMe×2), 5.75 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1^{I}), 5.45 (s, 1H, C*H* of 4-methoxybenzylidene), 4.55 (dd, 1H, $J_{2,3}$ 10.5, $J_{3,4}$ 8.04 Hz, H-3^{I}), 4.50 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1^{II}), 4.44 (dd, 1H, $J_{1,2}$ 8.5, $J_{2,3}$ 11.0 Hz, H-2^{I}), 4.30–4.22 (m, 2H, H-6^{II}a, 3^{I}-OH), 4.17 (d, 1H, $J_{3,4}$ 3.0 Hz, H-4^{II}), 4.14–4.08 (m, 1H, H-6^{I}a), 4.06–3.97 (m, 2H, H-6^{I}b, H-6^{II}b), 3.86 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4^{I}), 3.79 (s, 3H, O*Me*), 3.76–3.67 (m, 5H, H-5^{I}, H-2^{II}, O*Me*), 3.59 (ddd, 1H, $J_{2,3}$ 9.5, $J_{3,OH}$ 9.5, $J_{3,4}$ 3.5 Hz, H-3^{II}), 3.49 (bs, 1H, H-5^{II}), 2.44 (d, 1H, $J_{3,OH}$ 9.5 Hz, 3^{II}-OH), 2.34 (d, 1H, $J_{2,OH}$ 2.5 Hz, 2^{II}-OH), 1.08 (s, 9H, *Me*$_3$ of *tert*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.51, 168.04 (C=O), 160.11, 155.33, 150.98, 149.54, 136.20, 135.84, 135.65, 134.09, 133.49, 132.78, 131.70, 130.04, 129.68, 127.76, 127.66, 123.81, 118.80, 114.39, 113.49 (aromatic), 103.73 (C1^{II}), 101.17 (*C*H of 4-methoxybenzylidene), 97.42 (C1^{I}), 81.06 (C4^{I}), 75.32 (C3^{II}), 75.09 (C4^{II}), 72.81 (C5^{I}), 71.19 (C2^{II}), 69.75 (C3^{I}), 68.67 (C6^{II}), 66.93 (C5^{II}), 62.41 (C6^{I}), 56.37 (C2^{I}), 55.61, 55.22 (O*Me*), 26.81 (C*Me*$_3$ of *tert*-Bu), 19.36 (*C*Me$_3$ of *tert*-Bu); HRMS (FAB, positive ion mode, NBA) *m*/*z* = 956.3308 [M + Na]$^+$, calcd for $C_{51}H_{55}NO_{14}SiNa$, 956.3290.

4.4. 4-Methoxyphenyl 3-*O*-benzoyl-4,6-*O*-(4-methoxybenzylidene)-*β*-D-galactopyranosyl-(1→4)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (2).

To a solution of compound **8** (2.40 g, 2.57 mmol) in dry THF (50 mL) was added Bu_2SnCl_2 (78.1 mg, 0.26 mmol) and 1,2,2,6,6-pentamethylpiperidine (0.92 mL, 5.14 mmol), followed by kept stirring for 10 min at rt under Ar atmosphere. Benzoyl chloride (0.36 mL, 2.57 mmol) was added dropwise to the mixture at rt under Ar atmosphere. After stirring for 48 h, MeOH was added to quench excess reagent, and the mixture was evaporated under reduced pressure. The residue was diluted with $CHCl_3$, and washed with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/EtOAc, 1:0 to 0:1, v/v, linear gradient) to afford **2** (1.95 g, 1.88 mmol, 73%) as colorless amorphous.

$[\alpha]_D^{23}$ +23.9 (*c* 1.0, $CHCl_3$); R_f 0.41 (*n*-hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.13–6.69 (m, 27H, aromatic), 5.75 (d,1H, $J_{1,2}$ 8.0 Hz, H-1^{I}), 5.41 (s, 1H, C*H* of 4-methoxybenzylidene), 5.01 (dd, 1H, $J_{2,3}$ 10.0, $J_{3,4}$ 3.5 Hz, H-3^{II}), 4.60 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1^{II}), 4.54 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 8.6 Hz, H-3^{I}), 4.50–4.41 (m, 2H, H-2^{I}, H-4^{II}), 4.27 (m, 1H, H-6^{II}a), 4.23 (s, 1H, 3^{I}-OH), 4.14–3.98 (m, 4H, H-2^{II}, H-6^{I}a, H-6^{I}b, H-6^{II}b), 3.86 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 8.5 Hz, H-4^{I}) 3.82–3.70 (m, 7H, H-5^{I}, O*Me*×2), 3.59 (s, 1H, H-5^{II}), 2.17 (d, 1H, $J_{2,OH}$ 4.0 Hz, 2^{II}-OH), 1.09 (s, 9H, *Me*$_3$ of *tert*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.55, 168.13, 166.45 (C=O), 160.03, 155.39, 151.03, 135.94, 135.69, 134.16, 133.48, 133.35, 132.85, 131.79, 130.16, 129.98, 129.83, 129.77, 129.65,

128.53, 127.87, 127.73, 127.53, 123.67, 123.41, 118.80, 114.44, 113.49 (aromatic), 104.03 ($C1^{II}$), 100.73 (*C*H of 4-methoxybenzylidene), 97.48 ($C1^{I}$), 81.94 ($C4^{I}$), 75.40 ($C5^{I}$), 74.25 ($C3^{II}$), 73.31 ($C4^{II}$), 69.87 ($C3^{I}$), 68.69 ($C2^{II}$), 68.56 ($C6^{II}$), 66.81 ($C5^{II}$), 62.79 ($C6^{I}$), 56.24 ($C2^{I}$), 55.66, 55.29 (O*Me*), 26.88 (C*Me*$_3$ of *tert*-Bu), 19.38 (*C*Me$_3$ of *tert*-Bu) ; HRMS (FAB, positive ion mode, NBA) *m*/*z* = 1037.3693 $[M]^+$, calcd for $C_{58}H_{59}NO_{15}Si$, 1037.3654.

4.5. 4-Methoxyphenyl 3-*O*-benzoyl-4,6-*O*-(4-methoxybenzylidene)-*β*-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (10).

Compound **2** (817 mg, 787 μmol) was added to a solution of **9** (497 mg, 944 μmol) in anhydrous CH_2Cl_2 (10 mL), and then diluted with anhydrous Et_2O (20 mL). The mixture was kept stirring at rt for 30 min under Ar atmosphere in the presence of activated powdered molecular sieves (MS) AW 300 (1.00 g). *N*-Iodosuccinimide (443 mg, 1.97 mmol) was added to the mixture, followed by cooling down to −78 °C under Ar atmosphere. Triflic acid (13.8 μL, 141 μmol) in anhydrous Et_2O (124 μL) was added dropwise to the mixture. After stirring for 1 h, excess amount of Et_3N was added to terminate the reaction. After kept stirring for 15 min, the mixture was filtered through a bed of Celite, diluted with $CHCl_3$, washed successively with 5 wt% aq $Na_2S_2O_3$, satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a bed of Celite, and concentrated under reduced pressure. The residue was subjected to silica gel column

chromatography (*n*-hexane/EtOAc, 2:1, v/v, containing 0.1% Et_3N), providing pure **10** (867 mg, 596 μmol, 76%) as a white solid.

$[\alpha]_D^{23}$ −10.2 (*c* 0.64, $CHCl_3$); mp 106–107 °C; R_f 0.28 (*n*-hexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.20–6.64 (m, 42H, aromatic), 5.55 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1^{I}), 5.52 (s, 1H, C*H* of 4-methoxybenzylidene), 5.13–5.07 (m, 2H, H-1^{III}, H-3^{III}), 4.91–4.84 (m, 2H, H-3^{I}, H-5^{II}), 4.76–4.69 (m, 2H, H-2^{I}, H-1^{II}), 4.61 (s, 2H, -C*H*$_2$Ph), 4.53–4.25 (m, 6H, H-4^{I}, H-6^{I}a, H-4^{III}, H-6^{III}a, -C*H*$_2$Ph), 4.19–4.10 (m, 2H, H-2^{III}, -C*H*$_2$Ph), 4.10–3.96 (m, 3H, H-6^{I}b, H-6^{III}b, H-3^{II}), 3.71 (s, 3H, O*Me*), 3.69–3.62 (m, 2H, H-5^{I}, H-2^{II}), 3.59–3.48 (m, 4H, O*Me*, -C*H*$_2$Ph), 3.42 (s, 1H, H-5^{III}), 3.21 (s, 1H, H-4^{II}), 2.38 (d, 1H, $J_{2,OH}$ 3.0 Hz, 2^{III}-OH), 1.13 (s, 9H, *Me*$_3$ of *tert*-Bu), 1.08 (d, 3H, H-6^{II}, $J_{5,6}$ 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.28, 166.35 (C=O), 159.96, 155.37, 151.18, 139.56, 139.48, 138.16, 136.11, 135.44, 134.29, 133.88, 133.53, 132.29, 130.28, 130.00, 129.96, 129.80, 128.63, 128.57, 128.39, 128.29, 128.23, 128.17, 128.05, 127.98, 127.93, 127.85, 127.78, 127.66, 127.46, 127.39, 127.25, 127.12, 127.07, 127.02, 126.78, 123.76, 118.83, 114.44, 113.39 (aromatic), 101.78 (C1^{III}), 99.72 (*C*H of 4-methoxybenzylidene), 98.19 (C1^{II}), 97.89 (C1^{I}), 79.14 (C3^{II}), 78.77 (C4^{II}), 76.00 (C2^{II}), 74.90 (*C*H$_2$Ph), 74.61 (C4^{I}), 74.36 (C3^{III}), 73.64 (C4^{III}), 73.42 (C5^{I}), 73.01 (*C*H$_2$Ph), 72.41 (C3^{I}), 71.47 (*C*H$_2$Ph), 69.63 (C2^{III}), 69.08 (C6^{III}), 66.63 (C5^{III}), 66.45 (C5^{II}), 61.79 (C6^{I}), 56.81 (C2^{I}), 55.70, 55.06 (O*Me*), 26.99 (*Me*$_3$ of *tert*-Bu), 19.74 (*C*Me$_3$ of *tert*-Bu), 16.63 (C6^{II}) ; HRMS (FAB, positive ion mode, NBA) *m*/*z* = 1476.5502 $[M + Na]^+$, calcd for $C_{85}H_{87}NO_{19}SiNa$, 1476.5539.

4.6. 4-Methoxyphenyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (11).

Compound **2** (2.01 g, 1.94 mmol) was added to a solution of **9** (2.45 g, 4.66 mmol) in anhydrous CH_2Cl_2 (15 mL), and then diluted with anhydrous Et_2O (30 mL). The mixture was kept stirring at rt for 30 min under Ar atmosphere in the presence of activated powdered MS AW 300 (2.0 g). *N*-Iodosuccinimide (2.18 g, 9.70 mmol) was added to the mixture, and then it was cooled down to −40 °C under Ar atmosphere. Triflic acid (68 μL, 776 μmol) in anhydrous Et_2O was injected to the mixture. After stirring for 3 h, excess amount of Et_3N was added to terminate the reaction. The mixture was filtered through a bed of Celite, diluted with $CHCl_3$, washed successively with 5 wt% aq $Na_2S_2O_3$, satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (*n*-hexane/EtOAc, 1:0 to 0:1, v/v, linear gradient), providing pure **11** (3.03 g, 1.61 mmol, 83%) as a white solid.

$[\alpha]_D$ −28.2 (*c* 0.54, $CHCl_3$); mp 90–91 °C; R_f 0.79 (*n*-hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.10–6.68 (57H, m, aromatic), 5.57 (1H, d, $J_{1,2}$ 3.6 Hz, H-1^{III}), 5.46 (1H, s, -C*H* of *p*-methoxybenzylidene), 5.42 (1H, d, $J_{1,2}$ 8.0 Hz, H-1^{I}), 5.18 (1H, d, $J_{1,2}$ 8.0 Hz, H-1^{II}), 5.13 (1H, dd, $J_{2,3}$ 10.0, $J_{3,4}$ 3.8 Hz, H-3^{II}), 4.98 (1H, d, J_{gem} 11.8 Hz, -CH_2Ph), 4.91 (1H, m, H-5^{IV}), 4.75–4.73 (2H, m, H-2^{I}, H-3^{I}), 4.67 (1H, d, $J_{1,2}$ 4.0 Hz, H-1^{IV}), 4.62 (1H, d, J_{gem} 11.6 Hz, -CH_2Ph), 4.57–4.49 (5H,

m, -C*H*$_2$Ph×4, H-4^{I}), 4.45–4.29 (7H, m, H-4^{II}, H-2^{II}, H-6^{II}b, -C*H*$_2$Ph×4), 4.21 (1H, m, H-5^{III}), 4.16 (1H, m, H-6^{I}a), 4.05–3.98 (4H, m, H-6^{II}a, H-2^{III}, H-3^{IV}, -C*H*$_2$Ph), 3.76 (3H, s, O*Me*), 3.71–3.65 (2H, m, H-6^{I}b, H-2^{IV}), 3.55–3.52 (4H, m, O*Me*, H-3^{III}), 3.45 (1H, d, $J_{3,4}$ 3.2 Hz, H-4^{III}), 3.43 (1H, d, J_{gem} 12.4 Hz, -C*H*$_2$Ph), 3.33 (1H, m, H-5^{II}), 3.20 (1H, m, H-5^{I}), 3.09 (1H, s, H-4^{IV}), 1.30 (1H, d, $J_{5,6}$ 7.2 Hz, H-6^{III}), 1.19 (1H, d, $J_{5,6}$ 6.4 Hz, H-6^{IV}), 1.11 (9H, s, *Me*$_3$ of *tert*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.61, 159.97, 155.59, 151.32, 139.74, 139.57, 138.95, 138.78, 138.45, 138.19, 136.06, 135.15, 133.093, 133.71, 132.32, 130.18, 130.09, 129.94, 129.89, 129.70, 128.88, 128.46, 128.39, 128.33, 128.30, 128.27, 128.21, 128.18, 128.11, 128.04, 127.93, 127.82, 127.71, 127.57, 127.44, 127.37, 127.34, 127.10, 127.08, 127.05, 126.97, 126.65, 119.18, 114.45, 113.43 (C=O, aromatic), 99.86 (C1^{II}), 99.83 (*C*H of *p*-methoxybenzylidene), 98.75 (C1^{IV}), 98.41 (C1^{I}), 98.36 (C1^{III}), 79.48 (C4^{III}), 79.38 (C3^{IV}), 78.73 (C4^{IV}), 77.96 (C3^{III}), 77.55 (C4^{I}), 76.61 (C2^{III}), 76.16 (C3^{II}), 75.99 (C5^{I}), 75.07, 74.73 (*C*H$_2$Ph), 73.30 (C4^{II}), 73.28 (*C*H$_2$Ph), 73.09 (*C*H$_2$Ph), 72.94 (C3^{I}, *C*H$_2$Ph), 72.83 (C2^{IV}), 72.31 (C2^{II}), 71.38 (*C*H$_2$Ph), 69.14 (C6^{II}), 67.51 (C5^{III}), 66.84 (C5^{IV}), 66.33 (C5^{II}), 61.47 (C6^{I}), 56.92 (C2^{I}), 55.84, 55.10 (O*Me*), 26.87 (*Me*$_3$ of *tert*-Bu), 19.74 (*C*Me$_3$ of *tert*-Bu), 16.39 (C6^{III}), 16.31 (C6^{IV}); HRMS (FAB, positive ion mode, NBA) *m*/*z* = 1892.7506 [M + Na]$^+$, calcd for $C_{112}H_{115}NO_{23}SiNa$, 1892.7527.

4.7. 4-Methoxyphenyl 2,4,6-tri-*O*-acetyl-3-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-

glucopyranoside (12).

Compound **10** (0.43 g, 294 μmol) was dissolved in the mixture of dry MeOH (4.0 mL) and dry THF (4.0 mL) followed by addition of $Pd(OH)_2$ on activated carbon (20%, 200 mg). After stirring at rt under H_2 atmosphere for 10 h, the mixture was filtered through filter paper, followed by concentration under reduced pressure. To a solution of the residue in pyridine (8 mL) was added Ac_2O (350 μL, 3.70 mmol) under dry atmosphere at rt overnight, and methanol was added to quench excess reagents. The mixture was concentrated and coevaporated with toluene under reduced pressure. The residue was dissolved in $CHCl_3$, and washed with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Rf 75 system, *n*-hexane/EtOAc, 1:0 to 0:1, v/v, linear gradient) to afford **12** (153 mg, 116 μmol, 39%) as colorless amorphous.

$[\alpha]_D^{30}$ −42.7 (*c* 0.05, $CHCl_3$); R_f 0.32 (*n*-hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 7.95–6.69 (23H, m, aromatic), 5.60 (d, 1H, $J_{3,4}$ 3.2 Hz, H-4^{III}), 5.55 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1^{I}), 5.42 (s, 1H, H-4^{III}), 5.29–5.02 (m, 5H, H-3^{II}, H-5^{II}, H-1^{III}, H-2^{III}, H-3^{III}), 4.98 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1^{II}), 4.87–4.82 (m, 2H, H-3^{I}, H-2^{II}), 4.58–4.51 (m, 2H, H-2^{I}, H-6^{III}a), 4.37–4.30 (m, 2H, H-4^{I}, H-6^{III}b), 3.91–3.84 (m, 1H, H-5^{I}), 3.73 (s, 3H, O*Me*), 3.53 (bd, 1H, $J_{5,6}$ 10.0 Hz, H-5^{III}), 2.14–1.80 (m, 18H, Ac), 1.27 (d, 3H, $J_{5,6}$ 6.0 Hz, H-6^{II}), 1.12 (s, 9H, Me_3 of *tert*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.87, 170.73, 170.48, 170.42, 169.80, 169.05, 165.32 (C=O), 155.57, 150.98, 136.13, 135.89, 134.56, 133.60, 130.25, 130.04, 129.94, 128.70, 128.23, 128.15, 127.84, 123.81, 118.83, 114.54

(aromatic), 99.92 ($C1^{III}$), 97.74 ($C1^{I}$), 95.45 ($C1^{II}$), 75.56 ($C5^{I}$), 74.17 ($C4^{I}$), 72.00 ($C3^{III}$), 71.60 ($C4^{II}$), 71.48 ($C3^{I}$), 71.36 ($C5^{III}$), 69.35 ($C2^{III}$), 68.30 ($C3^{II}$), 67.94 ($C2^{II}$), 67.07 ($C4^{III}$), 64.37 ($C5^{II}$), 61.19 ($C6^{I}$), 61.10 ($C6^{III}$), 56.60 ($C2^{I}$), 55.74 (O*Me*), 27.01 (Me_3 of *tert*-Bu), 20.95, 20.87, 20.81, 20.67, 20.62 (Ac), 19.46 (CMe_3 of *tert*-Bu), 16.10 ($C6^{II}$); HRMS (ESI, positive ion mode) *m*/*z* = 1340.4334 $[M + Na]^+$, calcd for $C_{68}H_{75}NO_{24}SiNa$, 1340.4360.

4.8. 2,4,6-Tri-*O*-acetyl-3-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-D-glucopyranose (13).

Compound **12** (153 mg, 116 μmol) was dissolved in a mixed solution of CH_3CN-H_2O (8.0 mL – 2.0 mL) followed by addition of cerium(IV) ammonium nitrate (CAN) (190 mg, 348μmol). After stirring at rt for 6 h, the mixture was concentrated under reduced pressure to remove CH_3CN. The residue was dissolved in $CHCl_3$, washed successively with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with CH_3Cl/EtOAc (1:0 to 0:1, v/v, linear gradient, Rf 75 system) to afford **13** (86 mg, 70.9 μmol, 61%) as a yellowish amorphous powder. $[\alpha]_D^{28}$ −22.2 (*c* 0.1, $CHCl_3$); R_f 0.56 (CH_3Cl/EtOAc, 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 7.94–7.41 (19H, m, aromatic), 5.58 (d, 1H, $J_{3,4}$ 3.2 Hz, H-4^{III}), 5.39 (d, 1H, $J_{3,4}$ 3.2 Hz, H-4^{II}), 5.29–5.16 (m, 3H, H-1^{I}, H-3^{II}, H-2^{III}), 5.13–5.00 (m, 3H, H-1^{III}, H-5^{II},), 5.03 (dd, 1H, $J_{2,3}$ 10.0, $J_{3,4}$ 10.0 Hz, H-3^{III}), 4.95 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1^{II}), 4.84–4.77 (m, 2H, H-3^{I}, H-2^{II}), 4.54 (dd, 1H, $J_{5,6a}$ 6.5,

$J_{6a,6b}$ 11.2 Hz, H-6^{III}a), 4.33–4.10 (m, 3H, H-4^{I}, H-6^{III}b, H-2^{I}), 4.04 (m, 2H, H-6^{I}a, H-6^{I}b), 3.84–3.79 (m, 1H, H-5^{III}), 3.47 (m, 1H, H-5^{I}), 2.66 (d, 1H, $J_{1,OH}$ 8.2 Hz, 1-OH), 2.13–1.85 (m, 18H, Ac), 1.25 (d, 3H, $J_{5,6}$ 6.0 Hz, H-6^{II}), 11.5 (s, 9H, C*Me*$_3$ of *tert*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.89, 170.77, 170.48, 170.27, 169.82, 169.12, 165.35 (C=O), 136.26, 135.61, 134.55, 133.62, 133.45, 132.46, 130.34, 130.12, 129.77, 129.15, 128.73, 128.21, 127.89, 123.77 (aromatic), 99.86 (C1^{III}), 95.30 (C1^{II}), 92.86 (C1^{I}), 75.79 (C5^{I}), 74.19 (C4^{I}), 72.04 (C3 ^{III}), 71.64 (C4^{II}), 71.26 (C5^{III}, C3^{I}), 69.36 (C2^{III}), 68.28 (C3^{II}), 68.05 (C2^{II}), 67.02 (C4^{III}), 64.37 (C5^{II}), 61.37 (C6^{I}), 61.09 (C6^{III}), 58.58 (C2^{I}), 27.12 (C*Me*$_3$ of *tert*-Bu), 20.99, 20.92, 20.84, 20.73, 20.71, 20.65 (Ac), 19.55 (*C*Me$_3$ of *tert*-Bu), 16.12 (C6^{II}); HRMS (ESI, positive ion mode) *m*/*z* = 1234.3911 $[M + Na]^+$, calcd for $C_{61}H_{69}NO_{23}SiNa$, 1234.3927.

4.9. 2,4,6-Tri-*O*-acetyl-3-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate (14).

To a solution of compound **13** (32 mg, 26.4 μmol) in dry CH_2Cl_2 (5.0 mL) was added trichloroacetonitrile (53 μL, 527 μmol). After stirring at 0 °C under Ar atmosphere for 30 min, DBU (1 μL, 7.9 μmol) was added, then the reaction mixture was kept stirring at 0 °C under Ar atmosphere for 5 h. The mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane-ethyl acetate containing 0.5% Et_3N, 1:0 to 0:1, v/v, linear gradient,

Rf 75 system) to afford **14** (30 mg, 22.1 μmol, 83%) as colorless amorphous.

$[\alpha]_D^{27}$ −42.7 (*C* 0.1, $CHCl_3$); R_f 0.41 (*n*-hexane/EtOAc 1:1 containing with Et_3N); ^1H NMR ($CDCl_3$, 400 MHz, TMS): δ 8.55 (s, 1H, -CN*H*CCl_3), 7.96–7.30 (m,19H, aromatic), 6.36 (d, 1H, $J_{1,2}$ 8.8 Hz, H-1^I), 5.60 (d, 1H, $J_{3,4}$ 3.2 Hz, H-4^{III}), 5.42 (d, 1H, $J_{3,4}$ 2.8 Hz, H-4^{II}), 5.31 (dd, 1H, $J_{1,2}$ 10, $J_{2,3}$ 10 Hz, H-2^{III}), 5.24–5.19 (m, 2H, H-1^{III}, H-3^{II}), 5.16–5.12 (m, 2H, H-3^{III}, H-5^{II}), 5.01 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1^{II}), 4.91 (t, 1H, $J_{2,3}$ =$J_{3,4}$=8.7 Hz, H-3^I), 4.82 (dd, 1H, $J_{1,2}$ 3.9, $J_{2,3}$ 10.9 Hz, H-2^{II}), 4.65–4.52 (m, 2H, H-2^I, H-6^{III}a), 4.40–4.31 (m, 2H, H-4^I, H-6^{III}b), 4.08 (bs, 2H, H-6^Ia, H-6^Ib), 3.86 (m, 1H, H-5^{III}), 3.66–3.60 (m, 1H, H-5^I), 2.13, 2.12, 2.09, 2.08, 1.93, 1.84 (s×6, 18H, Ac), 1.28 (d, 3H $J_{5,6}$ 6.4 Hz, H-6^{II}), 1.15 (s, 9H, *Me*$_3$ of *tert*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.86, 170.82, 170.42, 170.21, 169.77, 169.03, 165.30, 160.73 (C=O, -*C*N$HCCl_3$), 136.14, 135.38, 134.59, 133.60, 133.47, 131.95, 130.24, 130.02, 129.75, 128.69, 128.20, 127.80, 123.71 (aromatic), 99.95 (C1^{III}), 95.39 (C1^{II}), 93.62 (C1^I), 90.47 (-*C*Cl_3), 76.06 (C5^I), 73.95 (C4^I), 71.98 (C3^{III}), 71.56 (C4^{II}), 71.43 (C5^{III}), 71.20 (C3^I), 69.31 (C2^{III}), 68.22 (C3^{II}), 68.09 (C2^{II}), 67.10 (C4^{III}), 64.38 (C5^{II}), 61.18 (C6^{III}), 60.09 (C6^I), 55.58 (C2^I), 26.98 (C(*C*H_3)$_3$ of *tert*-Bu), 20.95, 20.89, 20.81, 20.65, 20.61 (Ac), 19.55 (*C*(CH_3)$_3$ of *tert*-Bu), 16.09 (C6^{II}); HRMS (ESI, positive ion mode) *m*/*z* = 1377.2974 $[M + Na]^+$, calcd for $C_{63}H_{69}N_2O_{23}SiCl_3Na$, 1377.3024.

4.10. 2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethyl 2,4,6-tri-*O*-acetyl-3-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-

butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (15).

To a solution of compound **14** (40 mg, 29.8 μmol) in dry CH_2Cl_2 (5.0 mL) was added 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethanol (19 mg, 88.5 μmol) and activated 4Å molecular sieves (MS4A, 80 mg). After stirring at −50 °C under Ar atmosphere for 30 min, TMSOTf (2 μL, 8.85 μmol) was added to the mixture, followed by stirring at −50 °C under Ar atmosphere for 8 h. After the reaction was completed, the reaction mixture was neutralized by addition of Et_3N, filtered through a Celite bed, and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, and washed with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 1:0 to 0:1, v/v, Rf 75 system, linear gradient) to afford **15** (20 mg, 14.2 μmol, 48%) as colorless amorphous.

$[\alpha]_D^{29}$ −44.4 (*c* 0.1, $CHCl_3$); R_f 0.31 (*n*-hexane/EtOAc 2:3); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 7.95–7.36 (m,19H, aromatic), 5.58 (d, 1H, $J_{3,4}$ 3.2 Hz, H-4^{III}), 5.40 (d, 1H, $J_{3,4}$ 2.4 Hz, H-4^{II}), 5.28 (dd, 1H, $J_{1,2}$ 8.4, $J_{2,3}$ 10.0 Hz, H-2^{III}), 5.22–5.17 (m, 2H, H-1^{III}, H-3^{II}), 5.13–5.07 (m, 3H, H-1^{I}, H-3^{III}, H-5^{II}), 4.95 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1^{II}), 4.82 (dd, 1H, $J_{1,2}$ 4.0, $J_{2,3}$ 10.9 Hz, H-2^{II}), 4.77 (t, 1H, $J_{2,3}$ =$J_{3,4}$=9.9 Hz, H-3^{I}), 4.55 (dd, 1H, $J_{5,6a}$ 6.7, $J_{6a,6b}$ 11.6 Hz, H-6^{III}a), 4.35–4.22 (m, 3H, H-2^{I}, H-4^{I}, H-6^{III}b), 4.07–3.98 (m, 2H, H-6^{I}a, H-6^{I}b), 3.89–3.83 (m, 2H, H-5^{III}, PEG), 3.65–3.25 (m, 16H, H-5^{I}, PEG), 2.12, 2.10, 2.06, 1.91, 1.82 (s×6, 18H, Ac), 1.25 (d, 3H, $J_{5,6}$ 6.4 Hz, H-6^{II}), 1.15 (s, 9H, *Me*$_3$ of *tert*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.91, 170.89, 170.51, 170.29, 169.83, 169.12, 165.36

(C=O), 136.23, 135.50, 134.48, 133.62, 133.46, 132.25, 130.29, 130.07, 129.79, 129.16, 128.73, 128.24, 127.85, 123.68 (aromatic) , 99.93 ($C1^{III}$), 98.18($C1^{I}$), 95.36 ($C1^{II}$), 75.44 ($C5^{I}$), 74.38 ($C4^{I}$), 72.06 ($C3^{III}$), 71.68 ($C4^{II}$), 71.54 ($C3^{I}$), 71.31 ($C5^{III}$), 70.72, 70.64, 70.62, 70.54, 70.20, 70.16 (PEG), 69.45 ($C2^{III}$), 68.53 (PEG), 68.32 ($C3^{II}$), 68.04 ($C2^{II}$), 67.11 ($C4^{III}$), 64.33 ($C5^{II}$), 61.18 ($C6^{I}$, $C6^{III}$), 56.71 ($C2^{I}$), 50.79 (PEG), 27.07 (C*Me*$_3$ of *tert*-Bu), 20.98, 20.95, 20.85, 20.71, 20.67 (Ac), 19.54 (*C*Me$_3$ of *tert*-Bu), 16.14 ($C6^{II}$); HRMS (ESI, positive ion mode) *m*/*z* = 1435.5026 $[M + Na]^+$, calcd for $C_{69}H_{84}N_4O_{26}SiNa$, 1435.5041

4.11. 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-β-D-glucopyranoside (16).

Compound **15** (51 mg, 36.8 μmol) was suspended in dry MeOH (5.0 mL) followed by the addition of *ca.* 28 wt-% MeONa in MeOH (3 μL, 19.7 μmol). After stirring at rt under dry atmosphere overnight, the reaction mixture was neutralized by the addition of Dowex 50W-X4 (H^+ form), filtered through cotton, and concentrated under reduced pressure. The residue dissolved in EtOH (5.0 mL) was added $NH_2NH_2 \cdot H_2O$ (10 μL, 205.8 μmol). After stirring at 90 °C for 7 h, reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in pyridine (5.0 mL) followed by addition of Ac_2O (65 μL, 687.6 μmol) and DMAP (3 mg, 24.6 μmol). After stirring at rt under dry atmosphere for 36 h, MeOH was added to quench excess reagents, followed by

concentration under reduced pressure. The residue was dissolved in $CHCl_3$, and washed with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography eluting with CH_3Cl/MeOH (1:0 to 6:1, v/v, Rf 75 system, linear gradient). The obtained compound was dissolved in dry THF (3.0 mL) followed by the addition of AcOH (5 µl, 91.8 µmol) and 1M TBAF in THF (207 µl, 207 µmol). After stirring at rt under Ar atmosphere for 72 h, the reaction mixture was concentrated under reduced pressure and extracted with $CHCl_3$, washed with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with $CHCl_3$/MeOH (1:0 to 6:1, v/v, linear gradient, Rf 75 system) to afford the compound **16** (21 mg, 20.5 µmol, 56%, 4 steps) as colorless amorphous.

$[\alpha]_D^{26}$ −71.4 (*c* 0.2, $CHCl_3$); R_f 0.24 ($CHCl_3$/MeOH, 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 6.31 (d, 1H, $J_{2,NHAc}$ 9.4 Hz, N*H*Ac), 5.42–5.38 (m, 3H, H-1^{II}, H-4^{II}, H-4^{III}), 5.22 (dd, 1H $J_{2,3}$ 11.0, $J_{3,4}$ 3.4 Hz, H-3^{II}), 5.10–4.98 (m, 4H, H-2^{II}, H-5^{II}, H-2^{III}, H-3^{III}), 4.73 (d, 1H, $J_{1,2}$ 7.28 Hz, H-1^{III}), 4.67 (d, 1H, $J_{1,2}$ 8.40 Hz, H-1^{I}), 4.50 (dd, 1H, $J_{5,6a}$ 6.2, $J_{6a,6b}$ 11.4 Hz, H-6a^{III}), 4.32 (dd, 1H, $J_{5,6b}$ 7.9, $J_{6a,6b}$ 11.4 Hz, H-6b^{III}), 4.03–3.90 (m, 4H, H-2^{I}, H-4^{I}, H-6^{I}a, H-5^{III}), 3.85–3.54 (m, 16H, H-3^{I}, H-6^{I}b, PEG), 3.45–3.39 (m, 2H, PEG), 3.28–3.24 (m, 1H, H-5^{I}), 2.30 (dd, 1H, $J_{6a,OH}$ 3.96, $J_{6Ib,OH}$ 9.6 Hz, ^{I}6-OH), 2.19, 2.14, 2.13, 2.08, 2.05, 1.98, 1.97, 1.95 (s×8, 24H, Ac), 1.19 (d, 3H $J_{5,6}$ 6.5 Hz, H-6^{II}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.70, 171.15, 170.87, 170.67, 170.64, 170.14, 169.79, 169.26 (C=O),

102.11 ($C1^{I}$), 100.40 ($C1^{III}$), 95.58($C1^{II}$), 75.45 ($C5^{I}$), 74.55 ($C4^{I}$), 73.76 ($C5^{III}$), 71.73 ($C4^{III}$, PEG), 71.09, 71.05 ($C3^{I}$, $C3^{III}$), 70.99, 70.69, 70.67, 70.52, 70.10 (PEG), 69.47 ($C2^{III}$), 68.59 (PEG), 68.11 ($C2^{II}$, $C3^{II}$), 67.05 ($C4^{II}$), 64.14 ($C5^{II}$), 60.87 ($C6^{I}$), 60.59 ($C6^{III}$), 55.97 ($C2^{I}$), 50.76 (PEG), 23.35, 21.26, 20.96, 20.86, 20.83, 20.81, 20.76, 20.70 (Ac), 15.97 ($C6^{II}$); HRMS (ESI, positive ion mode) *m*/*z* = 1047.3740 $[M + Na]^+$, calcd for $C_{42}H_{64}N_4O_{25}Na$, 1047.3757.

4.12. Triethylammonium {2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-6-*O*-sulfonato-β-D-glucopyranoside} (17).

Compound **16** (28 mg, 27.3 μmol) was dissolved in dry DMF (3.0 mL) and Et_3N (600 μL). After stirring at 55 °C under Ar atmosphere for 20 min, the reaction mixture was added to $SO_3{\cdot}NMe_3$ (145 mg, 934 μmol). After stirring at 55 °C for 72 h, MeOH (1 mL) was added to quench excess reagents, and evaporated under reduced pressure. The residue was purified by LH-20 size exclusion column chromatography eluting with MeOH to afford **17** (30 mg, 24.9 μmol, 91%) as colorless amorphous. $[\alpha]_D^{23}$ −83.8 (*c* 0.07, MeOH); R_f 0.17 ($CHCl_3$/MeOH 10:1); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.46 (1H, bs, SO_3H), 6.43 (d, 1H, $J_{2,NHAc}$ 9.6 Hz, N*H*Ac), 5.45 (bs, 1H, H-4^{III}), 5.39 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1^{II}), 5.36 (bd, 1H, $J_{3,4}$ 3.0 Hz, H-4^{II}), 5.26 (dd, 1H, $J_{2,3}$ 10.9, $J_{3,4}$ 3.3 Hz, H-3^{II}), 5.10–4.97 (m, 5H, H-2^{II}, H-3^{III}, H-5^{II}, H-1^{III}, H-2^{III}), 4.60 (d, 1H, $J_{1,2}$ 8.40 Hz, H-1^{I}), 4.44 (dd, 1H, $J_{5,6a}$ 5.8, $J_{6a,6b}$ 11.2 Hz, H-6^{III}a), 4.32 (bs, 2H, H-6^{I}a, H-6^{I}b), 4.26 (dd, 1H, $J_{5,6b}$ 8.7, $J_{6a,6b}$ 11.1 Hz, H-6^{III}b), 4.05–

3.93 (m, 3H, H-2^{I}, H-5^{III}, PEG), 3.80–3.54 (m, 14H, PEG), 3.47–3.42 (m, 4H, H-3^{I}, H-4^{I}, H-5^{I}, PEG), 3.20 (6H, m, N(CH_2CH$_3$)$_3$), 2.17, 2.14, 2.12, 2.08, 2.06, 1.96, 1.95, 1.94 (s×8, 24H, Ac), 1.40 (t, 9H, J 7.3 Hz, N(CH$_2$CH_3)$_3$), 1.20 (d, 3H, $J_{5,6}$ 6.5 Hz, H-6^{II}); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.60, 171.26, 170.83, 170.61, 169.83, 169.80, 169.79, 169.76 (C=O), 102.04 (C1^{I}), 99.66 (C1^{III}), 95.53 (C1^{II}), 74.63 (PEG), 73.79 (C3^{I}, C5^{I}), 73.43 (C5^{III}), 71.83 (C4^{II}), 71.65 (PEG), 71.29 (C3^{III}), 70.88 (PEG), 70.72 (C4^{I}), 70.65, 70.61, 70.46, 70.06 (PEG), 69.44 (C2^{III}), 68.47 (PEG), 68.20 (C2^{II}), 67.94 (C3^{II}), 67.25 (C4^{III}), 64.91 (C6^{I}), 64.30 (C5^{II}), 60.64 (C6^{III}), 55.46 (C2^{I}), 50.78 (PEG), 46.71 (N(*C*H$_2$CH$_3$)$_3$), 23.30, 21.22, 21.02×2, 20.88, 20.83, 20.77, 20.69 (Ac), 15.97 (C6^{II}), 8.83 (N(CH$_2$*C*H$_3$)$_3$): HRMS (ESI, negative ion mode) *m*/*z* = 1103.3360 [M − HNEt$_3$]$^-$, calcd for C$_{48}$H$_{63}$N$_4$O$_{28}$S, 1103.3350.

4.13. 4-Methoxyphenyl 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→2)-4,6-di-*O*-acetyl-3-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (18).

To a solution of compound **11** (1.00 g, 0.53 mmol) in 20.0 mL of THF–MeOH (1:1,v/v) was added Pd(OH)$_2$-C (20%, 0.25 g, 1.78 mmol). After stirring at rt under H_2 for 10 h, the reaction mixture was filtered through a Celite bed, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dry pyridine (10.0 mL), followed by addition of DMAP (64 mg 0.53 mmol) and Ac$_2$O (1.0 mL, 10.6 mmol). After stirring at rt under dry atmosphere for 24 h, MeOH was added to quench

excess reagents, and then concentrated and coevaporated with toluene under reduced pressure. The residue was dissolved in $CHCl_3$, and washed with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography eluting with *n*-hexane/EtOAc (1:2, v/v, containing 0.5% Et_3N) to afford **18** (562 mg, 0.36 mmol, 68%) as colorless amorphous.

$[\alpha]_D^{27}$ −110.1 (*c* 0.03, $CHCl_3$); R_f 0.63 (*n*-hexane/EtOAc, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.89–7.32, 7.23–6.74 (23H, m, aromatic), 5.51 (bd, 1H, $J_{3,4}$ 3.4 Hz, H-4^{II}), 5.45 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1^{I}), 5.40 (bd, 1H, $J_{3,4}$ 2.7 Hz, H-4^{III}), 5.26–5.09 (7H, m, H-1^{IV}, H-4^{IV}, H-3^{III}, H-3^{II}, H-1^{II}, H-2^{IV}, H-5^{II}), 4.97–4.81 (m, 4H, H-1^{III}, H-3^{IV}, H-2^{III}, H-3^{I}), 4.59 (dd, 1H, $J_{1,2}$ 8.6, $J_{2,3}$ 10.0 Hz, H-2^{I}), 4.53–4 .40 (m, 3H, H-4^{I}, H-6^{II}a, H-5^{IV}), 4.30 (dd, 1H, $J_{5,6}$ 7.4, $J_{6a,6b}$ 11.4 Hz, H-6^{II}b), 4.23–4.15 (m, 2H, H-6^{I}a, H-6^{I}b), 3.92 (bt, 1H, $J_{1,2}$=$J_{2,3}$=9.0 Hz, H-2^{II}), 3.85–3.80 (m, 1H, H-5^{II}), 3.75 (s, 3H, O*Me*), 3.47–3.43 (m, 1H, H-5^{I}), 2.15, 2.11, 2.09, 2.08, 2.07, 1.92, 1.86, 1.72 (s×8, 24H, Ac), 1.27–1,24 (m, 6H, H-6^{III}, H-6^{IV}), 1.16 (s, 9H, *Me*$_3$ of *tert*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.00, 170.88, 170.67, 170.40, 170.15, 169.88, 169.85, 169.61, 169.15 (C=O), 155.69, 1150.94, 135.99, 135.41, 134.55, 133.90, 133.46, 132.04, 130.04, 129.99, 129.93, 129.96, 128.90, 128.27, 128.15, 127.89, 127.86 (aromatic), 99.86 (C1^{II}), 98.16 (C1^{I}), 97.72 (C1^{IV}), 95.92 (C1^{III}), 75.42 (C5^{I}), 74.21 (C2^{II}), 74.07 (C3^{II}), 73.04 (C4^{I}), 72.47 (C3^{I}), 71.70 (C4^{III}), 71.20 (C5^{II}), 71.06 (C4^{IV}), 68.23 (C3^{III}), 67.98 (C3^{IV}), 67.67 (C2^{III}), 67.27(C4^{II}), 66.88 (C2^{IV}), 65.41 (C5^{IV}), 64.41 (C5^{III}), 61.14, 61.08 (C6^{I}, C6^{II}), 56.83 (C2^{I}), 55.80 (O*Me*), 27.16 (*Me*$_3$ of *tert*-Bu), 21.06, 20.97, 20.82, 20.73, 20.69×2, 20.67, 20.34 (Ac),

19.43 (*C*Me$_3$ of *tert*-Bu), 15.59, 15.52 (C6^{III}, C6^{IV}); HRMS (ESI, positive ion mode) *m*/*z* = 1570.5151 [M + Na]$^+$, calcd for $C_{78}H_{89}NO_{30}SiNa$, 1570.5136.

4.14. 2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-(1→2)-4,6-di-*O*-acetyl-3-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate (19).

Compound **18** (562 mg, 0.36 mmol) was dissolved in a mixed solution of CH_3CN (8.0 mL)–H_2O (2.0 mL) followed by addition of CAN (592 mg, 1.08 mmol). After stirring at rt for 2 h, the reaction mixture was extracted with $CHCl_3$, washed successively with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 30:1, containing 0.5% Et_3N) to afford the corresponding anomer-free compound (440 mg). To a solution of this compound (440 mg) in dry CH_2Cl_2 (10 mL) was added CCl_3CN (290 μL, 2.90 mmol). After stirring at 0 °C under Ar for 15 min, DBU (13 μL, 87 μmol) was added to the mixture. After kept stirring for 4 h, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/EtOAc, 3:1, containing 0.5% Et_3N) to afford **19** (314 mg, 0.20 mmol, 2 steps, 56%) as colorless amorphous.

$[\alpha]_D^{27}$ −77.4 (*c* 0.5, $CHCl_3$); R_f 0.57 ($CHCl_3$/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.58 (s, 1H, N*H*), 7.90–7.32 (19H, m, aromatic), 6.32 (d, 1H, $J_{1,2}$ 8.8 Hz, H-1^I), 5.51 (bd, 1H, $J_{3,4}$ 3.6 Hz,

H-4^{II}), 5.39 (bd, 1H, $J_{3,4}$ 2.8 Hz, H-4^{III}), 5.26–5.24 (m, 2H, H-1^{IV}, H-4^{IV}), 5.23–5.16 (m, 2H, H-3^{II}, H-3^{III}), 5.14-5.07 (m, 3H, H-5^{III}, H-1^{II}, H-2^{IV}), 5.02–4.95 (m, 2H, H-3^{IV}, H-1^{III}), 4.94–4.84 (m, 2H, H-3^{I}, H-2^{III}), 4.63 (dd, 1H, $J_{1,2}$ 8.9, $J_{2,3}$ 10.2 Hz, H-2^{I}), 4.53–4.44 (m, 2H, H-4^{I}, H-6^{II}a), 4.42–4.36 (m, 1H, H-5^{IV}), 4.33-4.18 (m, 3H, H-6^{I}a, H-6^{I}b, H-6^{II}b), 3.92 (dd, 1H, $J_{1,2}$ 8.1, $J_{2,3}$ 9.9 Hz, H-2^{II}), 3.80–3.75 (m,1H, H-5^{II}), 3.62–3.58 (m, 1H, H-5^{I}), 2.12, 2.11, 2.09, 2.08, 2.07, 1.93, 1.86, 1.71 (s×8, 24H, Ac), 1.28–1.24 (m, 6H, H-6^{III}, H-6^{IV}), 1.16 (s, 9H, C*Me*$_3$ of *tert*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.97, 170.86, 170.53, 170.38, 170.13, 169.86, 169.61, 168.05, 165.23, 160.74 (C=O), 136.03, 135.40, 134.65, 133.87, 133.57, 132.19, 131.45, 130.09, 130.01, 129.57, 128.95, 128.72, 128.20, 127.88, 123.72 (aromatic, *C*=NH), 100.01 (C1^{II}), 97.80 (C1^{IV}), 95.89 (C1^{III}), 94.08 (C1^{I}), 90.48 (*C*Cl_3), 76.03 (C5^{I}), 74.39 (C2^{II}), 73.97 (C3^{II}), 72.99 (C4^{I}), 72.12 (C3^{I}), 71.65 (C4^{III}), 71.25 (C5^{II}), 71.15 (C4^{IV}), 68.14 (C3^{III}), 67.86 (C3^{IV}), 67.83 (C2^{III}), 67.33 (C4^{II}), 67.02 (C2^{IV}), 65.57 (C5^{IV}), 64.42 (C5^{III}), 61.14, 61.08 (C6^{I}, C6^{III}), 55.73 (C2^{I}), 27.14 (C*Me*$_3$ of *tert*-Bu), 21.00, 20.98, 20.82, 20.70, 20.68, 20.65, 20.64, 20.34 (Ac), 19.66 (*C*Me$_3$ of *tert*-Bu), 16.14, 15.73 (C6^{III}, C6^{IV}); HRMS (ESI) *m*/*z* = 1340.4334 [M + Na]$^+$, calcd for $C_{68}H_{75}NO_{24}SiNa$, 1340.4360.

4.15. 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→2)-4,6-di-*O*-acetyl-3-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (20).

To a solution of compound **19** (314 mg, 200 μmol) and 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethanol (65 mg, 0.30 mmol) in dry CH_2Cl_2 (5.0 mL) was added activated MS4A. The mixture was kept stirring at −50 °C for 15 min under Ar atmosphere, followed by addition of TMSOTf (11 μL, 59 μmol). After stirring at −50 °C for 30 min, Et_3N was added to terminate the reaction. The mixture was filtered through a Celite bed, and the filtrate was washed successively with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/EtOAc 1:2, v/v, containing 0.5% Et_3N) to afford **20** (262 mg, 159 μmol, 80%) as colorless amorphous.

$[\alpha]_D^{25}$ −73.6 (*c* 0.1, $CHCl_3$); R_f 0.39 (*n*-hexane/EtOAc 2:3); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.90–7.36 (19H, m, aromatic), 5.50 (bd, 1H, $J_{3,4}$ 3.8 Hz, H-4^{II}), 5.38 (bd, 1H, $J_{3,4}$ 3.0 Hz, H-4^{III}), 5.26–5.08 (m, 7H, H-1^{IV}, H-4^{IV}, H-3^{III}, H-3^{II}, H-1^{I}, H-5^{III}, H-3^{IV}), 5.02 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1^{I}), 4.98–4.93 (m, 2H, H-2^{IV}, H-1^{III}), 4.87 (dd, 1H, $J_{1,2}$ 4.0, $J_{2,3}$ 11.0 Hz, H-2^{III}), 4.78 (t, 1H, $J_{2,3}$=$J_{3,4}$=9.7 Hz, H-3^{I}), 4.50–4.38 (m, 3H, H-5^{IV}, H-6^{II}a, H-4^{I}), 4.36–4.26 (m, 2H, H-2^{I}, H-6^{II}b), 4.20 (bs, 2H, H-6^{I}a, H-6^{I}b), 3.95–3.88 (m, 2H, H-2^{II}, PEG), 3.82–3.78 (m, 1H, H-5^{II}), 3.70–3.23 (m, 16H, H-5^{I}, PEG), 2.11, 2.10, 2.08×2, 2.07, 1.92, 1.87, 1.73 (s×8, 24H, Ac), 1.27–1.24 (m, 6H, C6^{III}, C6^{IV}), 1.16 (s, 9H, *Me*$_3$ of *tert*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.96×2, 170.88, 170.67, 170.38, 170.13, 169.86×2, 169.63, 165.22×2 (C=O), 136.06, 135.47, 134.46, 133.88, 133.52, 132.40, 130.06, 130.01, 129.56, 128.94, 128.73, 128.22, 127.87, 123.61 (aromatic), 99.88 (C1^{II}), 98.50 (C1^{I}), 97.63 (C1^{IV}), 95.81 (C1^{III}), 75.30

($C5^{I}$), 74.07 ($C2^{II}$, $C3^{II}$), 73.28 ($C4^{I}$), 72.51 ($C3^{I}$), 71.72 ($C4^{III}$), 71.14 ($C5^{II}$), 71.07($C4^{IV}$), 770.87, 70.83, 70.76, 70.72, 70.66, 70.61, 70.55, 70.15, 70.10, 68.88 (PEG), 68.19 ($C3^{III}$), 68.03 ($C2^{IV}$), 67.75 ($C2^{III}$), 67.30 ($C4^{II}$), 66.93 ($C3^{IV}$), 65.41 ($C5^{IV}$), 64.34 ($C5^{III}$), 61.27 ($C6^{I}$), 61.04 ($C6^{II}$), 56.87 ($C2^{I}$), 50.80 (PEG), 27.15 (C*Me*$_3$ of *tert*-Bu), 21.01, 20.96, 20.83, 20.70×2, 20.68×2, 20.37 (Ac), 19.61 (*C*Me$_3$ of *tert*-Bu), 16.14, 15.65 ($C6^{III}$,$C6^{IV}$); HRMS (ESI) *m*/*z* = 1665.5807 $[M + Na]^+$, calcd for $C_{79}H_{98}N_4O_{32}SiNa$, 1665.5831.

4.16. 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl-(1→4)-[2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)]-6-*O*-*tert*-butyldiphenylsilyl-2-acetamido-2-deoxy-β-D-glucopyranoside (21).

To a solution of compound **20** (262 mg, 159 μmol) in MeOH (5.0 mL) was added MeONa in MeOH solution (*ca.* 28 wt%; 32 μL, 159 μmol). After stirring at rt for 2 h, DOWEX 50W-X8 (H^+ form) was added to neutralize the reaction system, and then filtered through cotton, concentrated under reduced pressure to obtain the crude mixture (203 mg). To a solution of the mixture (164 mg, 136 μmol) in EtOH (4.0 ml) was added $NH_2NH_2{\cdot}H_2O$ (33 μL, 681 μmol). After stirring at 90 °C for 13 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in pyridine (5.0 mL), followed by addition of Ac_2O (192 μL, 2.04 mmol) and DMAP (8 mg, 68.0 μmol). After stirring at rt under dry atmosphere overnight, MeOH (1 mL) was added to quench excess reagents, and the mixture was concentrated with toluene under reduced pressure. The

residue was dissolved in $CHCl_3$, washed with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (MeOH/EtOAc, 1:30, v/v, containing 1% Et_3N) to afford **21** (151 mg, 101 μmol, 64%) as colorless amorphous.

$[\alpha]_D^{25}$ −115.5 (*c* 0.24, $CHCl_3$); R_f 0.51 ($CHCl_3$/MeOH, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.76–7.70, 7.42–7.32 (m, 10H, aromatic), 6.11 (d,1H, $J_{2,NH}$ 8.6 Hz, N*H*), 5.39–5.37 (m, 2H, H-1^{IV}, H-4^{III}), 5.33–5.28 (m, 2H, H-4^{I}, H-1^{III}), 5.24 (dd, 1H, $J_{2,3}$ 11.0, $J_{3,4}$ 3.0 Hz, H-3^{III}), 5.17 (bs, 1H, H-4^{IV}), 5.07–4.95 (m, 5H, H-1^{II}, H-2^{III}, H-3^{IV}, H-2^{IV}, H-5^{III}), 4.92 (dd, 1H, $J_{2,3}$ 10.0, $J_{3,4}$ 3.5 Hz, H-3^{II}),4.61 (d, 1H, $J_{1,2}$ 7.4 Hz, H-1^{I}), 4.45 (dd, 1H, $J_{5,6a}$ 6.4, $J_{6a,6b}$ 11.5 Hz, H-6^{II}a), 4.32–4.20 (m, 3H, H-4^{I}, H-6^{II}b, H-5^{IV}), 4.15–4.04 (m, 2H, H-6^{I}a, H-6^{I}b), 3.93-3.86 (m, 4H, H-2^{I}, H-3^{I}, PEG×1), 3.78-3.59 (m, 14H, H-2^{II}, H-5^{II}, PEG×6), 3.42–3.39 (m, 2H, PEG×1), 3.16–3.12 (m, 1H, H-5^{I}), 2.18, 2.14, 2.13, 2.11, 2.05×2, 1.99, 1.96, 1.95, 1.91 (s×10, 3H×10, Ac×10), 1.17–1.06 (m, 15H, H-6^{IV}, H-6^{III}, *Me*$_3$ of *tert*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.64, 171.37, 170.90, 170.66, 170.60×2, 170.39, 170.24, 169.86, 169.80 (C=O), 136.05, 135.46, 133.61, 132.47, 129.89, 128.07, 127.81 (aromatic), 101.48 (C1^{I}), 100.56 (C1^{II}), 96.64 (C1^{III}), 96.09 (C1^{IV}), 75.37 (C5I), 73.61 (C2^{II}), 73.40 (C3^{II}), 73.08 (C4^{I}), 71.79 (C4^{III}), 71.36, 71.07 (PEG), 70.97 (C4^{IV}), 70.94 (C5^{II}), 70.68, 70.67, 70.55, 70.07 (PEG), 68.19 (C3^{III}), 68.10 (C3^{I}, C2^{IV}), 68.04 (C2^{I}), 67.96 (C2^{III}), 67.72 (C3^{IV}), 67.33 (C4^{II}), 65.03 (C5^{IV}), 64.06 (C5^{III}), 61.36 (C6^{I}), 61.04 (C6^{II}), 50.78 (PEG), 27.10 (*Me*$_3$ of *tert*-Bu), 23.48, 21.33, 20.96, 20.84×2, 20.83×3, 20.76, 20.71, (Ac), 19.57 (*C*Me$_3$ of *tert*-Bu) 16.14, 15.71 (C6^{III}, C6^{IV});

HRMS (ESI, positive ion mode) *m/z* = 1510.6196 $[M + NH_4]^+$, calcd for $C_{68}H_{100}N_5O_{31}Si_1$, 1510.6172.

4.17. Sodium {2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl β-D-galactopyranosyl-(1→4)-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-6-*O*-sulfonato-β-D-glucopyranoside} (3).

To a solution of the compound **17** (30 mg, 24.9 μmol) in MeOH (3.0 mL) was added MeONa (*ca.* 28 wt-%) in MeOH (2 μL, 12.4 μmol). After stirring at rt overnight, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biogel P-2 gel column eluting with H_2O to afford **3** (13 mg, 15.6 μmol, 63%) as colorless amorphous.

$[\alpha]_D^{25}$ −37.5 (*c* 0.2, MeOH); R_f 0.51($CHCl_3$/MeOH/H_2O, 5:4:1); ^{1}H NMR (400 MHz, CD_3OD): δ 5.04 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1^{II}), 4.83–4.76 (m, 1H, H-5^{II}), 4.59 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1^{III}), 4.55 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1^{I}), 4.44 (dd, 1H, $J_{5,6a}$ 3.4, $J_{6a,6b}$ 10.8 Hz, H-6^{III}a), 4.31 (dd, 1H, $J_{5,6b}$ 2.5, $J_{6a,6b}$ 10.9 Hz, H-6^{III}b), 3.98–3.84 (m, 5H, H-2^{I}, H-3^{II}, H-4^{I}, PEG×1), 3.82 (d, 1H, $J_{3,4}$ 2.9 Hz, H-4^{III}), 3.79–3.61 (m, 18H, H-6^{I}a, H-6^{I}b, H-2^{II}, H-3^{I}, H-4^{II}, H-5^{III}, PEG×6), 3.56–3.1 (m, 2H, H-3 ^{III}, H-5^{I}), 3.47 (dd, 1H, $J_{1,2}$ 7.6, $J_{2,3}$ 9.6 Hz, H-2^{III}), 3.42–3.38 (m, 2H, PEG×1), 1.97 (s, 3H, Ac), 1.17 (d, 3H, $J_{5,6}$ 6.5 Hz, H-6^{II}); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.83 (C=O),103.61 (C1^{III}), 102.40 (C1^{I}), 100.15 (C1^{II}), 76.40 (C5^{I}), 76.27, 75.17, 75.07, 74.80, 73.72 (C4^{II}, C3^{III}, C5^{III}, C3^{I}, C4^{I}), 72.97 (C2^{III}), 71.51, 71.48, 71.44, 71.40, 71.35 (PEG), 71.15 (C3^{II}), 71.04 (PEG), 70.11 (C4^{III}), 69.98 (C2^{II}), 69.94 (PEG), 67.72 (C5^{II}), 66.96 (C6^{III}), 62.66 (C6^{I}), 56.71 (C2^{I}), 51.77 (PEG), 23.08 (Ac), 16.61 (C6^{II}); HRMS (ESI,

negative ion mode) *m*/*z* = 809.2626 [M − Na]$^-$, calcd for $C_{28}H_{49}N_4O_{21}S$, 809.2610.

4.18. 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl β-D-galactopyranosyl-(1→4)-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-β-D-glucopyranoside (4).

Compound **15** (51 mg, 36.1 μmol) was suspended in dry MeOH (3.0 mL) followed by the addition of *ca.* 28 wt-% MeONa in MeOH (5 μL, 32.9 μmol). After stirring at rt under dry atmosphere overnight, the reaction mixture was neutralized by the addition of Dowex 50W-X4 (H^+ form), filtered through cotton, and concentrated under reduced pressure. The residue dissolved in EtOH (4.0 mL) was added $NH_2NH_2{\cdot}H_2O$ (10 μL, 212.8 μmol). After stirring at 90 °C overnight, the reaction mixture was concentrated under reduced pressure. To a solution of the residue in pyridine (3.0 mL) was added Ac_2O (50 μL, 530.7 μmol). After stirring at rt under dry atmosphere for 36 h, MeOH (1 mL) was added to quench excess reagents, then concentrated with toluene under reduced pressure. The residue was purified by silica gel column chromatography (CH_3Cl/MeOH, 1:0 to 6:1, v/v, linear gradient, Rf 75 system). The obtained compound was dissolved in dry THF (3.0 mL) followed by the addition of AcOH (3 μL, 58.6 μmol) and 1M TBAF in THF (550 μl, 550 μmol). After stirring at rt under Ar atmosphere for 3 days, the reaction mixture was concentrated under reduced pressure and extracted with $CHCl_3$, washed with satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography ($CHCl_3$/Methnol, 1:0 to 6:1, v/v, linear gradient, Rf 75

system) to afford **16**. To a solution of **16** in MeOH (4.0 mL) was added MeONa in MeOH (*ca.* 28 wt-%, 6 μL, 40.9 μmol). After stirring at rt overnight, the reaction mixture was concentrated under reduced pressure. The residue was subjected to LH-20 size-exclusion column chromatography eluting with H_2O, and then to reversed phase column chromatography eluting with H_2O/MeOH (1:0 to 0:100, v/v, linear gradient, Rf 75 system) to afford **4** (4 mg, 5.47μmol, 15%, 5 steps) as colorless amorphous.

$[\alpha]_D^{24}$ −56.0 (*c* 0.04, MeOH); R_f 0.58 ($CHCl_3$/MeOH/H_2O, 5:4:1); ^{1}H NMR (400 MHz, CD_3OD): δ 5.03 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1^{II}), 4.86–4.81 (m, 1H, H-5^{II}), 4.54 (d, 1H, $J_{1,2}$ 7.5 Hz, H-1^{I}), 4.44 (d, 1H, $J_{1,2}$ 7.3 Hz, H-1^{III}), 3.95–3.84 (m, 6H, H-6^{III}a, H-4^{I}, H-2^{I}, H-3^{II}, PEG×1), 3.82–3.60 (m, 19H, H-4^{III}, H-6^{I}a, H-4^{II}, H-6^{III}b, H-6^{I}b, H-5^{III}, H-2^{II}, PEG×6), 3.54–3.35 (m, 6H, H-2^{III}, H-3^{III}, H-3^{I}, H-5^{I}, PEG×1), 1.97 (s, 3H, Ac), 1.18 (d, 3H, $J_{5,6}$ 6.6 Hz, H-6^{II}); ^{13}C NMR (CD_3OD, 100 MHz): δ 173.90 (C=O), 103.89 (C1^{III}), 102.40 (C1^{I}), 100.35 (C1^{II}), 77.42 (C5^{I}), 76.66 (C3^{I}, C5^{III}), 75.17 (C3^{II}), 74.90 (C3^{III}), 73.69 (C4^{II}), 72.75 (C2^{III}), 71.69, 71.62, 71.54, 71.51 (PEG), 71.22 (C4^{I}), 71.13 (PEG), 70.00 (C4^{III}), 69.94 (C2^{II}), 69.90 (PEG), 67.67 (C5^{II}), 62.77 (C6^{I}), 61.39 (C6^{III}), 57.38 (C2^{I}), 51.77 (PEG), 23.12 (Ac), 16.61 (C6^{II}); HRMS (ESI, positive ion mode) *m*/*z* = 753.3000 $[M + Na]^+$, calcd for $C_{28}H_{50}N_4O_{18}Na$, 753.3018.

4.19. 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl α-L-fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→4)-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-β-D-glucopyranoside

(5).

Compound **21** (24 mg, 16.1 μmol) was dissolved in THF (3 mL) followed by addition of AcOH (3 μl, 64.3 μmol) and TBAF (156 μL, 156 μmol). After stirring at rt under Ar atmosphere for 72 h, the reaction mixture was concentrated under reduced pressure and extracted with $CHCl_3$, washed successively with satd aq $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered through a Celite bed, and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography eluting with CH_3Cl/MeOH (1:0 to 6:1, v/v, linear gradient, Rf 75 system). To a solution of the obtained product in dry MeOH (3 mL) was added MeONa in MeOH (*ca.* 28 wt-%, 10 μL, 56.8 μmol). After stirring at rt overnight, the reaction mixture was added DOWEX 50W-X4 (H^+ form) to neutralize the reaction system, and then filtered and concentrated under reduced pressure. The residue was purified by LH20 column chromatography eluting with MeOH to afford **5** (8 mg, 9.1 μmol, 57%, 2 steps) as colorless amorphous. $[\alpha]_D^{22}$ −104.4 (*c* 0.01, MeOH); R_f 0.53 ($CHCl_3$/MeOH/water, 5:4:1); ^{1}H NMR (400 MHz, CD_3OD): δ 5.17 (d, 1H, $J_{1,2}$ 3.2 Hz, H-1^{IV}), 5.03 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1^{III}), 4.88–4.79 (m, 1H, H-5^{IV}), 4.54-4.51 (m, 2H, H-1^{I}, H-1^{II}), 4.22–4.16 (m, 1H, H-5^{III}), 3.95–3.61 (m, 29H, PEG×6, H-2^{I}, H-3^{I}, H-4^{I}, H-6^{I}a, H-6^{I}b, H-2^{II}, H-3^{II}, H-4^{II}, H-5^{II}, H-6^{II}a, H-6^{II}b, H-2^{III}, H-3^{III}, H-4^{III}, H-2^{IV}, H-3^{IV}, H-4^{IV}), 3.47–3.43 (m, 1H, H-5^{I}), 3.39–3.35 (m, 2H, PEG×1), 1.97 (s, 3H, Ac), 1.26–1.21 (m, 6H, H-6^{III}, H-6^{IV}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.89 (C=O), 102.53, 102.21 (C1^{I}, C1^{II}), 102.14 (C1^{IV}), 100.36 (C1^{III}), 79.45, 77.45, 76.72, 76.64, 76.52, 75.30, 74.46, 73.71, 73.67, 71.87, 71.68, 71.60, 71.53,

71.25, 71.13, 70.79, 70.13, 69.96, 69.93 ($C5^{I}$, $C4^{I}$, $C5^{II}$, $C3^{I}$, $C4^{II}$, $C2^{II}$, $C3^{II}$, $C4^{II}$, $C2^{III}$, $C3^{III}$, $C2^{IV}$, $C3^{IV}$, $C4^{IV}$, PEG), 68.28 ($C5^{III}$), 67.65 ($C5^{IV}$), 62.94, 62.71 ($C6^{I}$, $C6^{II}$), 57.32 ($C2^{I}$), 51.78 (PEG), 23.12 (Ac), 16.86, 16.80 ($C6^{III}$, $C6^{IV}$); HRMS (ESI, positive ion mode) m/z = 899.3592 $[M + Na]^+$, calcd for $C_{34}H_{60}N_4O_{22}Na$, 899.3597.

4.20. A typical procedure for synchronous synthesis of 10 and 11.

Compound **2** (100 mg, 96.3 μmol) was added to a solution of **9** (90 mg, 170.9 μmol) in anhydrous CH_2Cl_2 (1.0 mL), and then diluted with anhydrous Et_2O (2.0 mL). The mixture was kept stirring at rt for 30 min under Ar atmosphere in the presence of activated MSAW 300 (100 mg). *N*-Iodosuccinimide (55 mg, 244.5 μmol) was added to the mixture, and then it was cooled down to −40 °C under Ar atmosphere. Triflic acid (1.7 μL, 19.3 μmol) in anhydrous Et_2O (100 μL) was injected to the mixture. After stirring for 1 h, excess amount of Et_3N was added to terminate the reaction. The mixture was filtered through a Celite bed, diluted with $CHCl_3$, washed successively with 5% aq $Na_2S_2O_3$, satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered through a Celite bed, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (*n*-hexane/EtOAc, 1:0 to 0:1, v/v, linear gradient, Rf75 system), providing **10** (69 mg, 48.4 μmol, 49%) and **11** (73 mg, 43.3 μmol, 45%).

Acknowledgments

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Supplementary data

^{1}H, H,H-COSY and ^{13}C NMR spectra of compounds **2**–**5**, **7**–**8**, **10**–**21** are provided as Supplementary data online version.

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